VIEWPOINT

Genes, Genetics, and Epigenetics: A Correspondence

C.-t. Wu and J. R. Morris

Over the past months, as this special issue took shape, the Editors of *Science* have monitored an exchange of seven letters initiated by three queries from M. Bacon. These queries concern the popular definitions of "genes," "genetics," and "epigenetics." Below, we reprint excerpts from these letters, referring interested readers to www.sciencemag.org/cgi/content/full/293/5532/1103/DC1 for the complete text and additional references.

Dear Editors,

How remarkable has been the progress of this new science called "genetics"! So many of the puzzles that have fueled the great debates of Heredity appear solved and scarcely can I believe the elegance of the solutions. To think that in so short a time from my own we will have witnessed progression from the Hippocratic and Darwinian theories of pangenesis to a capability of altering the very nature of hereditary material such that species can be intermingled! Here, I dare not linger but to bid you imagine my awe. My current state, however, is not just one of awe, for I am also adrift; words that I believe I know, or that are just now arriving at a comfortable definition, are not familiar to me when I chance across their use in the writings of your time. . . I will ask you, in particular, about three.

May I begin with "gene"? Is it true that the gene can be compleately and satisfactorily defined by a single chemical, the deoxyribonucleic acid, or DNA? I see it defined as such in your textbooks and newspapers and hear it so described both in formal lectures and in casual conversation. While it is delightful, though most unexpected, to see this word commonly mentioned (even among children at play!), is there no doubt that "gene" can be so simply defined? As you know, "gene" was first put forth for consideration a year ago by Wilhelm Johannsen, who does not at all employ it to indicate a chemical substance (*1*). Rather, Johannsen regards the "gene" from the standpoint of its consequences on inheritance and urges restraint in the imposition of theoretical and physical limitations. . .

My second query concerns the very word "genetics" itself. I see it not infrequently described with direct and near exclusive reference to genes, sometimes simply as "the study of genes," and even once as having come from the word "gene" (this latter claim being wholly untrue). Surely these simplifications are indefensible. If "genetics" is so tied to "genes," and "genes" are more often than not considered in terms of DNA, am I to learn that there will soon be complacency among geneticists that the definition of "genetics" rests so heavily on DNA? Here, I cannot hide my distress behind ignorance of events to come. Genetics is the study of Heredity and Variation. . . and I dare to predict that, even in your time, it will not be possible to reduce them to chemicals or isolable things.

Finally, then, I come to the word "epigenetics." This term surely brings to mind the process of epigenesis. As laid out by Casper Friedrich Wolff a century and a half ago and much before him by William Harvey, epigenesis encompasses the mysterious workings of Nature that allow structure to form de novo from the apparent structureless mass that results from the union of egg and sperm. Imagine, therefore, my surprise in learning that "epigenetics" will ultimately be understood as the study of changes in gene function that are heritable and that do not entail a change in DNA sequence! I am astonished that the two definitions bear so little resemblance to each other and that, yet again, my journey leads to the DNA chemical. What has been the logical progression from original to new? But more, I am perplexed by the definition. If there is something other than DNA that can be changed and that, importantly, produces consequences that are heritable, why do your colleagues define the gene with respect to only its DNA component? That is, should not the gene, when it is to be described by its chemical components (a task to which, I remind you, Johannsen would most certainly object!) be defined by all of its components rather than by only a portion of what is responsible for its role in the inheritance of traits? As you see, with this final query I come full circle to my original question: What is the gene?

M. Bacon, Traveller
9 January 1910

Dear M. Bacon,

[Your] questions concern what must appear to you as a nearly overwhelming preoccupation with DNA. . . As the history of how this happened may address some of your questions, our response will be in the context of a brief and necessarily biased timeline. . . Yours is a remarkable time. You are witnessing momentous arguments regarding the validity of immensely important theories, including the Darwinian theory of natural selection, the chromosome theory of August Weissman, the mutation theory of Hugo de Vries, the ancient theories of pangenesis and epigenesis (the theory of preformation having fallen much earlier), and, most recently, the Mendelian theory of inheritance and the chromosome theory as interpreted by Theodor Boveri and Walter Sutton. . .

C.-t. Wu and J. Morris, Boston, Massachusetts
13 October 2000

Dear C.-t. Wu and J. Morris,

Your letter arrived with this morning's post and has neither left my hand nor freed my mind since. The glimpse of the future which you offer is appreciated more than you may guess as my advanced age makes it unlikely that I will know this future in any other way. In this regard, your letter has been a second lifetime to me, and I am most grateful. Further, you are too kind to ask for my opinion. Of what use could my opinion be? However, as you have been more than generous with your thoughts. . . I will venture the following.

First, I am more than a little surprised that it will be studies of the bacteria and their viruses that will so soundly convince the community of the chemical nature of the gene. Will there be no demands for proof in a diversity of organisms. . .

But more importantly, you wish to know whether I think the definition of "genes" and even all of "genetics" in terms of the nucleic acid DNA is correct, whether I think the future's history will do justice to genetics. With apology but no reservation, I shall have to answer "No." I am immensely taken by the events forthcoming. . . yet still will I hold that all of Inheritance cannot lie neatly at the feet of four nitrogenous bases. Recall only the inquiry in my first letter regarding the definition of "epigenetics." Your "epigenetics" implies substances other than DNA that impinge on Heredity, and therefore, and again, why are these substances so soundly ignored by your chemists? What are these other substances?. . . If there are elements aside from DNA that are responsible for the inheritance

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of traits, I would urge that they be considered central to the particulate theory of the gene. . .
M. Bacon
3 February 1910

Dear M. Bacon,

You are surprised that the chemical nature of the gene. . . will be considered resolved prior to extensive confirmation in other organisms. A good deal of the explanation can be traced to the excitement of those years. . . that just as physics and chemistry rest on universal laws, heredity would follow laws, laws that transcend species barriers. . . For reasons of availability, ease of culture, and amenability to analysis, certain organisms will prevail and form a cadre of model organisms. . . As you might have guessed by now, model organisms will also be considered such because they will be among the best behaved (most "law" abiding) and therefore most permissive of study. In this way, model organisms will come to define an unavoidably limited and biased view of the living world, and organisms not within their ranks and phenomena not included in their biology will come to be viewed, perhaps all too readily, as exceptional, or will be eclipsed altogether.

This in mind, we would like next to better address the terms "gene," "genetics," and "epigenetics". . . Is your uneasiness not so much about how DNA came to play a central role, but more about why researchers will be so quick to accept and less than eager to question this tenet? Here, again, we should comment on the impact of the popular belief that heredity follows rules and that these rules can be determined from the study of model organisms. From our reading of history, the contribution of this viewpoint to the underappreciation of unusual findings will both sharpen the focus but narrow the breadth of genetics, encouraging ultimately the explicit definitions of "gene," "genetics," and "epigenetics." By way of illustration, we describe below four events or observations that we neglected to mention in our first letter. . . We will start with the studies of Mendel himself. . .

Moving on, we would like now to address specifically your interest in the etymology of "epigenetics". . . Our research takes us to 1942 and Waddington, who will suggest the term and its definition as the study of the relationship between genotype and phenotype (*2*). In his paper introducing "epigenetics," Waddington will begin with a mention of heredity or inheritance, the "subject-matter" of genetics, and then go on to contrast genetics with what he proposes to call "epigenetics," the study of the processes by which genotype gives rise to phenotype. . .

Waddington's definition will remain intact for several decades. In 1987, Robin Holliday. . . will write, "The properties of genes in higher organisms can be studied on two levels: first, the mechanism of their transmission from generation to generation, which is the central component of genetics and is well understood, and second, their mode of action during the development of the organism from the fertilized egg to adult, which is very poorly understood. The changes in gene activity during development are generally referred to as epigenetic. . ." (*3*, p. 163).

Seven years later, Holliday will. . . suggest two variations. . . First, Holliday will point out that changes in gene expression occur not only during development but also during the adult stage of an organism. . . Accordingly, he will suggest epigenetics to be the "study of the changes in gene expression, which occur in organisms with differentiated cells, and the mitotic inheritance of given patterns of gene expression" (*4*, p. 453). Holliday will emphasize that this definition "says nothing about mechanisms, so it can include all types of DNA-protein interactions, as well as changes at the DNA level. . ." (*4*, p. 453).

This new definition will also clearly raise a second issue, which is the notion of inheritance. . . How is this inheritance affected? Holliday will first remind us that DNA can undergo permanent changes in sequence during development and that such changes would be expected to be heritable through cell division. . . [He] will then move on to heritable changes in gene expression that can be reversed at a later stage, sometimes after meiosis. As most reversible changes in gene regulation are not expected to entail alterations of DNA, it is here that Holliday suggests his second variation. . . a "supplementary definition of epigenetics to include transmission of information from one generation to the next, other than the DNA sequence itself" (*4*, p. 454), in other words, "Nuclear inheritance which is not based on differences in DNA sequence" (*4*, p. 454).

So, here we are, at the brink of, but not quite arrived at, the definition of epigenetics which you have found so puzzling. There remains but one more step to reach this final destination, and that is the simplification, in the form of a fusion, of Holliday's two definitions. Specifically, the most current interpretation of epigenetics combines the concept of changes in gene expression and the implication of mitotic inheritance (from the first variation) with the use of DNA as a reference point and the implication of generational, including meiotic, inheritance (from the second variation) to give rise to our current definition: the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence.

This, then, is the outcome of our amateur research on the etymology of "epigenetics," although doubtless there are other interpretations and many more contributors to mention. . . As you have noted, although "epigenetics" is defined in terms of DNA, its clear message is that we must pay greater attention to things non-DNA.
C.-t. Wu and J. Morris
1 December 2000

Dear C.-t. Wu and J. Morris,

While I followed your progression from one tier of interpretation to the next. . ., scarcely can I accept the final definition as fair outcome of the journey. To begin, I do not understand the restriction of "epigenetics" to changes, per se, in gene expression as surely the mere "action" of genes is of sufficient consequence to merit note. Then, is not what you proffer in your conclusion as the fusion of two definitions but a hybrid most lacking? The intention of the first encompasses all changes in activity of the gene, those that do alter the DNA as well as those that do not. Quite in contrast, the second directs attention most especially to events that do not change the DNA. Why, therefore, do you disregard this difference in meanings and proceed to accept the second definition, modified but slightly, as an equitable fusion of both and a fitting end to your discourse?. . .

Equally puzzling is the departure from maintaining clear distinction between Epigenetics and Inheritance, the subject of Genetics. The boundary that Waddington and the younger Holliday will so deftly draw between these fields seems to me a sound and useful one; the Beasts are different and their loads not comparable. To mix them does much to confuse me. . . The study of Inheritance, called Genetics and as we know it in my day, is a field of endeavour born from the observation that traits can be inherited. Epigenetics is quite another matter for it will be the study of the process by which genotype produces phenotype. To then cut out portions of Genetics, to single out those forms of Inheritance that do not rest on the chemical DNA, and then to call upon these forms to define Epigenetics, does this not alter the fundamental meaning of Epigenetics even as it whittles away at the greater breadth of Genetics?. . .

Perhaps it is in further consideration of the gene that the original intention of Waddington may be sought and that the separation of Genetics and Epigenetics be justified and their definitions restored. If, as you say, the gene may change from one form to another, is then the gene the element before the change or after the change, or is it instead the core that persists unchanged? From all you have divulged to me, I see now that none from among these choices will do, for each regards the gene as an object, held still in time or held constant through time, even though your words argue that the true essence of the gene cannot be captured in time and is as much its Potential as it is its Substance. In this way, do we slight the

gene when we describe its chemistry without mention of its Capacity? It is here, in consideration of Capacity, that I am reminded of Epigenetics, for does not this word "Epigenetics" imply activity of the gene in development, and, by fulfillment of this activity, does not the gene make known its Capacities and therefore its complete character? I will submit, then, that Epigenetics, when used in reference to the gene only, be the study of the activities and the Capacities of the gene with no requirements or restrictions based on change or inheritance, that Inheritance be restored fully to the realm of Genetics, which concerns the transmission of traits from one individual to another either through simple cell division or the more elaborate sexual processes and all without regard to the particulars of mechanism, and that, finally, "gene" will continue to your time, entirely useful and adequately described as that which is responsible for the manifestation of traits, whatever its underlying chemical nature. "Gene," as we in my time use it, is a word most magnanimous and, by this attribute, most valuable. It accepts all manners of interpretation and, as we leave it unconstrained, so does it free us and goad us to seek further. Would not a word such as this be welcomed in your time also? Yet do I press you to return "gene" to its original meaning that it may again prove its full worth.

But you must find it odd, even disturbing, that after all you have shared with me I should return to interpretations so divested of stolen knowledge. . . Perhaps I am not prepared to move forward into your time of abundant knowledge for, where I sit, we are only just beginning to contemplate Possibilities. . .

M. Bacon
29 March 1910

Dear M. Bacon,

[We] would guess that Holliday would more than readily agree with you for he, himself, warned. . . against simplifying "epigenetics" to just one of his two definitions (*4*). . . As for the mixing of inheritance with epigenetics, here, too, we have benefited from your critique. Do you know, for instance, that epigenetics in our time enjoys a variety of definitions. . .? Another popular definition states that epigenetics concerns those forms of inheritance that do not follow the Rules of Mendel and, making no mention of gene expression, places epigenetics squarely and entirely within the realm of inheritance. From this, we wonder whether, by leaning the definition of "gene" on DNA and "genetics" on Mendel, we were caught off guard when "gene" and "genetics" became more complex, and then, in need of a name to unify outlying observations, we saw a solution in "epigenetics"; "epi," meaning "besides," "upon," or "over," would imply the existence of phenomena beyond the familiar. Yet, having read your letter, it is now clear to us that the drifting of epigenetics toward genetics may not be desirable. . ., and you will be pleased to know that Morgan will agree with you. He will contend in his "The theory of the gene" that in order to study heredity, a geneticist must first separate issues of inheritance from issues of development (*5*). . .

We leave you with a quotation from Bateson, taken from his 1926 paper on "Segregation". . . We believe that it may be to your liking as it seems to speak to. . . the importance of having Possibilities.

> "The growth of genetical science has been surprisingly rapid. To those who have not forgotten the period of stagnation which so long continued, such an activity can only be a source of satisfaction, as implying zeal both in observation and invention. We do well, however, to remember that that long spell of dulness from which we were so lately emancipated, ensued as the direct consequence of a too facile acquiescence in impermanent doctrines. Curiosity was too easily allayed. We are in no such danger yet, but the following pages may at least serve as a reminder that, even as regards the outline of genetical principles, finality has not been attained" (*6*, p. 201).

C.-t. Wu and J. Morris
18 January 2001

Dear C.-t. Wu and J. Morris,

I quite agree with the quotation from Bateson. And on this point, should I bring our correspondence to conclusion, for when I came to the end of your letter and put myself to test, I found there beginnings of the very acquiescence of which Bateson spoke! Though I have urged, and still do urge, Exploration in the truest sense of that word and count myself among the restless, I cannot deny that the knowledge you have shared has taken toll on the vista of what I think possible; reports that are in conflict with what you have imparted to me, yet would have otherwise brought pause and consideration, are now but quickly read and put aside. Where is my curiosity? What is my duty? While I am more than humbled by what will be accomplished, who is to say what trifling notions from my time will endure, will find their way to yours and then beyond, and there, in your future and against all predictions, make their mark? It is clear. My place is here, travelling forward and travelling best without set destination. In this way may I still hope to make a real contribution. Therefore, with heartfelt and final regards, and deepest gratitude, will I remain always

Yours most sincerely,
M. Bacon
16 May 1910

References and Notes

1. W. Johannsen, *Elemente der exakten Erblichkeitslehre* (Gustav Fischer, Jena, Germany, 1909).
2. C. H. Waddington, *Endeavour* **1**, 18 (1942).
3. R. Holliday, *Science* **238**, 163 (1987).
4. _____, *Dev. Gen.* **15**, 453 (1994).
5. T. H. Morgan, *Am. Nat.* **51**, 513 (1912).
6. W. Bateson, *J. Genet.* **16**, 201 (1926).

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