Genes, Genetics, and Epigenetics:

A Correspondence

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Over the past months, as this special issue took shape, the Editors of Science 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 the letters, an excerpted version of which appears in *Science*, vol. 293, pages 1103-5.

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. Even "gene" and "genetics," which have only recently and with heated discussion been brought into being, seem to have taken on different meanings (although here and there I am able still to find poignant reference to their original intentions). Will these words remain under disputation a near century after their invention? I will ask you, in particular, about three.

May I begin with "gene"? Is it true that the gene can be compleatly 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. Rather, Johannsen regards the "gene" from the standpoint of its consequences on inheritance and urges restraint in the imposition of theoretical and physical limitations. In Johannsen's words,

> "Es hat nie bezweifelt werden können, daß die Geschlechtszellen – die Gameten, wie man jetzt mit einem gemeinsamen Namen für Ei- und Spermazelle sagt – „etwas" enthalten, welches den Charakter des durch die Befruchtung gegründeten Organismus bedingt oder sehr wesentlich beeinflußt. Die Zygote – das Vereinigungsprodukt der beiden bei der Befruchtung beteiligten Gameten – enthält eben dasjenige, welches von den betreffenden Gameten bei der Vereinigung mitgebracht wurde. Dieses „etwas" in den Gameten bezw. in der Zygote, welches für den Charakter des Organismus wesentliche Bedeutung hat, nennt man gewöhnlich mit einem recht mehrdeutigen Ausdruck „Anlagen". Man hat viele andere Ausdrücke in Vorschlag gebracht, meistens leider in genauer Verbindung mit bestimmten hypothetischen Auffassungen. Das von DARWIN eingeführte Wort „Pangene" wird wohl am häufigsten statt „Anlagen" benutzt. Jedoch ist das Wort „Pangen" nicht glücklich gewählt, indem es eine Doppelbildung ist, die Stämme Pan (neutr. von Πας , all, jeder) und Gen (von γί–γ(ε)ν–ομαι, werden) enthaltend. Nur der Sinn dieses letzteren kommt hier in Betracht; bloß die einfache Vorstellung soll Ausdruck finden, daß durch „etwas" in den Gameten eine Eigenschaft des sich entwickelnden Organismus bedingt oder mitbestimmt wird oder werden kann. Keine Hypothese über das Wesen dieses „etwas" sollte dabei aufgestellt oder gestützt werden. Darum scheint es am einfachsten, aus DARWIN'S bekanntem Wort die uns allein interessierende letzte Silbe „Gen" isoliert zu verwerten, um damit das schlechte, mehrdeutige Wort „Anlage" zu ersetzen. Wir werden somit für „das Pangen" und die „Pangene" einfach „das Gen" und „die Gene" sagen. Das Wort Gen ist völlig frei von jeder Hypothese; es drückt nur die sichergestellte Tatsache aus, daß jedenfalls viele Eigenschaften des Organismus durch in den Gameten vorkommende besondere, trennbare und somit selbstständige „Zustände", „Grundlagen", „Anlagen" – kurz, was wir eben Gene nennen wollen – bedingt sind" (from Johannsen 1909, pages 123-124).

Hesitatingly, then, will I again ask whether the "gene" of Johannsen is the same as that which you describe as a molecule of DNA?

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. This word, "genetics," was put forth by William Bateson five years ago when, invited to produce a title for a professorship to be dedicated to the study of Heredity, he wrote to Professor Adam Sedgwick, "If the Quick Fund were used for the foundation of a Professorship relating to Heredity and Variation the best title would, I think, be "The Quick Professorship of the study of Heredity". No single word in common use quite gives this meaning. Such a word is badly wanted, and if it were desirable to coin one, "GENETICS" might do. Either expression clearly includes Variation and the cognate phenomena." Heredity and

Variation are processes of infinite complexity 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?

Very respectfully yours,
M. Bacon
Traveller
January 9, 1910

Dear M. Bacon,

The Editors of this journal have asked us to consider your questions. To begin, we must inform you that we are most certainly *not* historians of science, a fact which we are anxious for you to remember as you read on. I surmise that we have been contacted only because the editors are aware of our interest in the issues which you have outlined and perhaps also because we are involved in a course whose title includes the word "epigenetics" (although neither of us has ever been quite sure of the meaning of this word). Our qualifications, then, are simply genuine interest and unwarranted brashness. That being said, we are eager to begin a conversation with you and learn from your perspective even as we urge you to consult others more qualified than ourselves. [On this note, we confess that we are not fluent in German and have had to turn to our colleague Dr. Christine Hartmann for a translation of the quotation from Johannsen. For the convenience of those who, like us, are restricted to the English language, the translation we are using is given in Allen 1978, pp. 209–210)

Your letter focuses on three words. For each, your questions concern what must appear to you as a nearly overwhelming preoccupation with DNA, and more generally, with the chemical and physical nature of the "things" that make inheritance happen. Your perception is accurate. From your time forward, the drive to identify and purify the molecules responsible for heredity will intensify many times over and result in DNA moving steadily into the limelight. 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. Whether history justifies DNA capturing the lion's share of attention is a matter of opinion and we hope that by extending ours we will be rewarded with yours in return. We will suggest that the reason the gene is most frequently described in our time simply as a segment of DNA is not so much that this definition is correct but more because some time in and around your decade, there will be a conscientious shift in the philosophical approach to the basis of inheritance. More specifically, efforts to explain inheritance in terms of physical entities will become favored, and Johannsen's Gen "fully free from every hypothesis" will be transformed into a gene with mass and form and, therefore, perhaps limitations.

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. We will focus our discussion on the latter two theories.

At the time from which you are writing us, William Bateson is the most outspoken proponent of Gregor Mendel but is adamantly opposed to the chromosome theory, and Thomas Hunt Morgan is deeply skeptical of both. Morgan has argued that the simple Mendelian relationship between dominant and recessive characters cannot explain the innumerable variations in the manifestation of some traits, that the number of chromosomes present in the nucleus is far smaller than one would expect if each represents a single Mendelian character, and that if a single chromosome actually represents multiple characters, then the incidences of coupling between characters are far fewer than would be expected. But, perhaps most disturbing to both Morgan and Bateson is the idea that heredity can be encompassed in a material entity; it is simply inconceivable that such an entity can give rise to the intricacies of inheritance and the complexity of the developmental program. In spite of the cytological studies of Nettie M. Stevens and Edmund B. Wilson revealing linkage between gender and the X and Y chromosomes, Morgan is demanding evidence and Bateson is incredulous that chromosomes, so bland and terribly undynamic, can produce the miraculous events of development. In short, from where you are, both Morgan and Bateson are balking at the particulate theory of inheritance.

You may be astounded, therefore, to learn that within five years of your letter, Morgan will become the foremost proponent of both the Mendelian and chromosome theories! By July of your year, Morgan will be on the verge of publishing his finding that the X chromosome of Drosophila is associated with a trait (eye color) other than that of gender. One year more and Morgan will further claim that the X is also associated with traits concerning body pigmentation and wing structure. These findings will make it unreasonable to consider the X chromosome as a structure that merely "comes along with" sexual dimorphism and will force Morgan to acknowledge that the basis of heredity may well be intimately associated with a physical structure. In 1911, Morgan will publish that "What is most important, is the discovery that the X-chromosome contains not only one of the essential factors in sex determination, but also all other characters that are sex-limited in inheritance" (Morgan 1911, page 409).

In that same remarkable paper of 1911, Morgan will discuss several other fundamental observations of genes, including the basis for coupling between traits, the theory of recombination between genes on a single chromosome, the possibility that a single gene can influence more than one character, and the nature of gene mutations! These observations will convince Morgan that not only is the chromosome theory correct, but that Mendel was also on the mark. Most important for our discussion, however, is that the complete acceptance of both the Mendelian and chromosome theories will lead Morgan to accept the physical nature of the gene. He will write, "...segregation, the key note to all Mendelian phenomena, is to be found in the separation, during the maturation of the egg and the sperm, of material bodies (chemical substances) [Morgan's parenthetical statement] contained in the chromosomes" (Morgan 1911, page 383).

By 1915, Morgan, Alfred H. Sturtevant, Hermann J. Muller, and Calvin B. Bridges will publish their landmark treatise, *The Mechanism of Mendelian Heredity*, and then in 1917, Morgan will defend his stance elegantly in "The theory of the gene" published in *The American Naturalist*. Here, he will write, "So far I have spoken of the genetic factor as a unit in the germ plasm whose presence there is inferred from the character itself. Why, it may be asked, is it not simpler to deal with the characters themselves, as in fact Mendel did, rather than introduce an imaginary entity, the gene. There are several reasons why we need the conception of the gene" (Morgan 1917, page 517). At this point, Morgan lists cogent and compelling reasons for the concept of the gene and concludes with "All of this evidence has played a rôle in persuading us that the genes postulated for Mendelian inheritance have a real basis and that they are located in the chromosomes" (Morgan 1917, page 520). Thus will begin a new phase of genetics where emphasis will shift from discussions of whether genes exist, and in which genes are defined by their consequences on traits, to a fast-paced effort to determine the physical chemical nature of the gene, an effort that will quickly focus attention on the nucleic acid DNA.

Nucleic acids are already attracting much attention in your day. In fact, in December of your year, your contemporary Albrecht Kossel will be presented with the Nobel Prize in part for his work on nucleic acids. Our historians tell us that studies of the physicochemical basis of heredity, and nucleic acids in particular, stem back to about the time when Mendel was carrying out his genetic analyses. By the latter half of the 1800's cytologists and embryologists had revealed that the nucleus plays a key role during fertilization and described the intricate and telling behavior of chromosomes during cell division. Such studies would lead Wilhelm Roux to publish as early as 1883 that chromosomes are likely to be the basis of heredity, a proposal that had to await its union with the Mendelian theory of inheritance in order to be accepted.

Importantly, these studies also sparked the interest of chemists who set out to reveal the chemical nature of the nucleus. In 1871, Friedrich Miescher published his purification of "nuclein" from the nucleus and then demonstrated by 1889 that nuclein consists of two substances, protein and a new chemical which his student Richard Altmann termed "nucleic acid". The subsequent work of Albrecht Kossel and his colleagues, including Phoebus A. Levene and Walter Jones, on the nucleic acids is by your day already recognized as path breaking. Nucleic acids will be found to come in two forms, a deoxyribose containing form called deoxyribonucleic acid (DNA) and a ribose containing form called ribonucleic acid (RNA). Both forms will be also be shown to contain nitrogenous bases, where each base is covalently attached to a sugar, either a deoxyribose or a ribose, and phosphoric acid to make what is called a nucleotide. Three bases - adenine (abbreviated as A), guanine (G), and cytosine (C) - appear in both DNA and RNA, while thymine (T) appears only in DNA and uracil (U) appears only in RNA.

Yes, it is true. The DNA about which you have heard so much is a simple chemical. We understand that in your time protein is favored as the hereditary material because its unlimited variability in form and composition appears to be a perfect match for the intricacies of heritable traits. However, the tide will turn, albeit slowly. In 1928, Frederick Griffith will find that a nonpathogenic version of the deadly pneumococcus bacterium can be transformed into a pathogenic version simply by being exposed to a heat-killed preparation of a pathogenic strain. This observation will demonstrate that the genetic material capable of conferring pathogenicity is an inanimate substance that, furthermore, can be moved from one organism to another! Recognizing that the identity of the transforming material will reveal the chemical nature of the gene, Oswald T. Avery, Colin M. MacLeod, and Maclyn J. McCarty will initiate a study that will lead them to announce in 1944, and to the bewilderment of their colleagues, that the transforming material is almost certainly not protein but DNA instead.

This news will be met with passionate skepticism. The following years will see the development of revolutionary technologies and an acceleration of the race to determine the true chemical nature of the gene. In 1952, Alfred Hershey and Martha Chase will publish data that strongly implicate DNA as the infectious chemical of a bacteriophage, which is a virus that attacks bacteria. To most scientists and historians this experiment will unambiguously define the nature of the gene. It is DNA.

But how can DNA, a simple chemical composed of four kinds of nucleotides, effect heredity? A key step in resolving this issue will come from the publication of Erwin Chargaff in 1950. Prior to this publication, DNA will be viewed as either a tetramer of the four nucleotides or a polymer of such tetramers. Given such a structure, it will seem unlikely that DNA can provide the complex information carried by genes. Chargaff will undo this tetramer model through two observations.

First, Chargaff will demonstrate that the base composition of DNA varies from species to species, indicating that DNA cannot be a monotonous repetition of the four nucleotides. This discovery eventually will lead to the idea that DNA encodes genetic information in the form of a *non*monotonous sequence of the nucleotides. Chargaff's second contribution will come from his observation that G and C appear in equal proportions as do A and T. This discovery, known as the "Equivalence Rule," will allow the combined efforts of Rosalind Franklin, Maurice Wilkins, James Watson, and Francis Crick to reveal the structure of DNA as two polymers of nucleotides that are paired such that G's are matched with C's and A's are matched with T's. This model for the structure of DNA, and therefore of genes, will be published in 1953 by Watson and Crick in a paper that will be regarded as a milestone in the history of genetics. Not only will this model support the view that hereditary information lies in the order of the four bases, it will suggest templating as a solution to the question of how this genetic information can be replicated and transmitted from one generation to the next.

We hope that this very inadequate rendition of some of the ninety years between you and us will begin to explain why we are so preoccupied with DNA. Essentially, acceptance of the Mendelian and chromosome theories of inheritance and their promulgation by Morgan and his colleagues will establish the idea that the gene is particulate. Once this concept is accepted, great effort will be expended toward identifying the chemical nature of the gene, and once this task is accomplished, the gene (and all of genetics as well) will come to be defined in terms of a chemical, DNA. Do *you* think this stance correct? Will the course of history do justice to genetics? We would very much appreciate hearing first hand about your times and learning your opinion.

In closing, we leave you with this quote from Gunther Stent. It comes from a narrative in which he describes the progression of our understanding of heredity from your time to the dawning of what we now call molecular genetics: "The fundamental unit of classical genetics is an indivisible and abstract gene. The fundamental unit of molecular genetics, by contrast, is a concrete chemical molecule, the nucleotide, the gene being relegated to the role of a secondary unit aggregate comprising hundreds or thousands of nucleotides. For the classical geneticist, study of the detailed nature and physical identity of the gene, though undoubtedly of great intellectual interest, is not an essential part of his work. His theories on the mechanics of heredity and the experimental predictions to which these theories lead, are largely formal, and their success does not depend on knowledge of structures at the submicroscopic, or molecular, level where the genes lie. Despite the lack of understanding of what Muller called its "real core," classical genetics *had* been fantastically successful. It had raised our understanding of the living world to previously unknown heights of sophistication" (Stent 1971, page 23).

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

[1] The following is the translation by Dr. Hartmann of the quotation from W. Johannsen (1909, pages 123-124) found in the January 9th letter from M. Bacon. From the eighth sentence onward, it incorporates, with slight modifications, translations taken from Garland E. Allen (1978) and Elof A. Carlson (1966): There has been no doubt about that the gametes contain 'something' which is responsible for, or influences the character of the newly founded organism. The zygote, which results from the fusion of the gametes during fertilization contains the 'something' supplied by each of the gametes. This 'something' in the gametes or zygote, which is accountable for the character of the organism, is usually referred to as 'Anlage' – a very ambiguous term. Many other terms have been proposed which are unfortunately all associated with assumptions. The most commonly used term instead of 'Anlage' is 'pangen', which is derived from Darwin. However, the word 'pangen', is an unfortunate choice, since it is a combination of two Greek words (pan, meaning all, everybody; gen, meaning to become). Only the meaning of the latter is suitable to describe that 'something' in the gametes can or might be able to contribute to a trait of the developing organism. No hypothesis concerning the nature of this 'something' shall be put forward thereby or based thereon. Therefore it appears as most simple to use the last syllable 'gen' taken from Darwin's well-known word pangene since it alone is of interest to use, in order to replace the poor, and ambiguous word, 'Anlage'. Thus, we will say for 'pangen' and 'pangenes' simply 'gene' and 'genes'. The word gene is fully free from every hypothesis; it expresses only the safely proven fact that in any case many characteristics of the organism are conditioned by special,

separable and hence independent ‘conditions’, ‘Grundlagen’, ‘Anlagen’ – in short what we will call just ‘genes’ – which are present in the gametes.

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 comply; there is no other way, I fear, in which I can return the favor you have shown me. Therefore, with due respect to the years between us, and asking your tolerance before you read on, 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? My desk is overflowing with notes on Pisum, Oenothera, Hieracium, and too many other flowering plants (if not the plants themselves!), the poultry, rabbits, and moths of Bateson, the guinea-pigs of Castle, the sea urchin of Boveri, the beetle, the bug, the snail, and the starfish. What will become of the studies of these organisms? Or, will a few decades make clear that the bacteria of van Leeuwenhoek and their even smaller parasites are true and valid representatives of us all?

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 and foresee that I shall soon make my peace with the particulate theory, 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? It would be as if, upon discovery of a new flower, we chose first to celebrate its color and, consequently, by its color it became best and commonly defined. What person would not call foul if later this flower were found to have a most heady perfume but, the flower having been described first by its color, the perfume could not then be considered a feature of the flower? If there are elements aside from DNA that are responsible for the inheritance of traits, I would urge that they be considered central to the particulate theory of the gene.

But I have gone too far and now fear reproof. My only lamentable excuse would be that had the abominable English weather permitted me my usual afternoon walk, I would not have had the time to ramble on as such!

Respectfully,
M. Bacon

February 3, 1910

Dear M. Bacon,

If anyone should fear reproof, it would be ourselves. In our eagerness to relate the well-loved story of how DNA came to play a pivotal role in our understanding of heredity, we lost sight of the greater meaning of your questions. Not only did we fail to justify the apparent singular focus on DNA, our first letter, in and of itself, seems a fairly good example of that singularity of thought! We stand corrected. Here, then, is our second pass.

You are surprised that the chemical nature of the gene, as revealed by studies in bacteria and phage, 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 (and perhaps also of your times?) that just as physics and chemistry rest on universal laws, heredity would follow laws, laws that transcend species barriers. In 1942, Conrad H. Waddington, embryologist, geneticist, and evolutionist, will write, "Of all the branches of biology it is genetics, the science of heredity, which has been most successful in finding a way of analyzing an animal into representative units, so that its nature can be indicated by a formula, as we represent a chemical compound by its appropriate symbols" (Waddington 1942, page 18). This philosophy will permit researchers working with different organisms to synthesize their finding and greatly accelerate our understanding of genetic mechanisms. For reasons of availability, ease of culture, and amenability to analysis, certain organisms will prevail and form a cadre of *model* organisms, that is, organisms that are widely regarded as good and fair representatives of the living world. By mid-century, bacteria and their phage will have earned a prominent place among them.

The validity of model organisms will become generally accepted. By our day, model organisms will garner the bulk of research effort and monetary support in the arena of the basic biological sciences, and there will be no denying the tremendous amount of important and coherent information that will emerge from them. Moreover, because model organisms will be called upon to illustrate the principles of genetics and biology in classrooms throughout the world, they will have a significant role in setting the pace of our studies as well as the breadth of our knowledge. You will want at this point, we are sure, to learn that our model organisms actually do succeed in portraying the diversity of life. In fact, and of course, they do not. We are embarrassed to tell you how few organisms have reached the status of being models, and worse, that none of the organisms listed in your last letter are included among the select few. 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" for you have, understandably, maintained your challenge of our certainty in defining these words in terms of DNA. Our first letter attempted to explain the increasing focus on DNA as a consequence of a shift in the philosophical approach to genetics, a shift that will support the particulate view of the gene. It went on from there to recount the popular history of how DNA will be identified as the genetic material. We are now, however, clearer about your concerns and would like to return to our first letter to make amendments. 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 hope that you will find them interesting. At the least, they should illustrate how the quest for unifying themes may have influenced the history of genetic thought.

We will start with the studies of Mendel himself. While many will come to know of Mendel's work with Pisum and readily embrace his findings as the First and Second Laws, fewer will be aware that Mendel went on to work with Hieracium, where his laws for peas could not be so easily applied. Although we know today that the confounding progeny that Mendel obtained arose from a parthenogenetic pathway, this explanation was not obvious to Mendel. As his data failed to reveal any satisfying pattern of inheritance, it is not surprising that when Mendel was reintroduced in 1900 by your colleagues, it was essentially only his work on Pisum that survived well. (We are curious, are you or your colleagues aware of his work on Hieracium?) What the world will gain by this selective recovery of information is a sweeping acceptance of Mendelian Laws as well as a relatively unencumbered confirmation that heredity is governed by universal principles. What it will lose is that half of Mendel's work that would have urged some modicum of restraint in the adoption of laws and a heightened interest in the possibility of exceptions.

Our second example of an observation not fully appreciated will occur in the historic year of 1915, when Morgan's group will publish their hugely successful treatise, giving Mendelian laws and the chromosome theory a tangible framework. That same year will see the publication of another very insightful article. This one, however, will be largely ignored. In it, Bateson and Caroline Pellew will describe a peculiar observation (of Mendel's Pisum, no less) that will appear to violate the First Law of Mendel; the gene under study will change its character! The authors will write, "... the facts already established are so unusual that it seems desirable to make them generally known. So far as we are aware the case is as yet unique" (Bateson and Pellew 1915, page 13) and then later "The general course of the phenomena is evidently quite unlike anything with which we are familiar in ordinary Mendelian inheritance" (Bateson and Pellew 1915, page 30).

Today we recognize Bateson and Pellew's discovery as possibly the first observation of a fascinating phenomenon known as paramutation which, according to R. Alexander Brink, is "an interaction between alleles that leads to directed, heritable change at the locus with high frequency, and sometimes invariably, within the time span of a generation" (Brink 1973, page 129). Whether paramutation constitutes a true violation of the First Law is not of consequence here. What is relevant is that Bateson and Pellew's provocative study will fail to inspire serious reassessment of Mendelian theory and serves to illustrate the tremendous momentum that Mendelian law will have acquired by 1915.

Going forward three decades to our third example, we come to the experiments of Avery, MacLeod, and McCarty in 1944 and of Hershey and Chase in 1952. As explained in our first response, these studies will cause the burden of inheritance to be placed on DNA. Furthermore, bolstered by the dogma of model organisms and a belief in the generality of genetic mechanisms, they remain to this day the most elegant and frequently cited proof of DNA being the chemical nature of the gene, not just in bacteria and phage, but in organisms in general. In our own first letter to you, we rested our arguments on these studies with nary a caveat. Our point here is that we were wrong to have been so cavalier. First, we should have mentioned that although what is now called the Hershey-Chase paper will be considered proof that DNA is the genetic material, the authors themselves will stop short of that conclusion. Instead, they will caution their readers explicitly against extrapolating beyond the data: "The chemical identification of the genetic part must wait..." (Hershey and Chase 1952, page 54). And second, we should have acknowledged that, just as you have pressed, the gene is, in fact, *not* always DNA.

By 1956, a mere four years after the Hershey-Chase experiments, Heinz L. Fraenkel-Conrat and the team of Alfred Gierer and Gerhard Schramm will demonstrate that the genetic material of the tobacco mosaic virus is not DNA, but RNA instead. Today, RNA viruses are as intensely studied as are DNA viruses, although it is true that we fail to mention RNA nearly as often as we do DNA when we speak of the chemical basis of the gene. Even the role of protein in heredity is enjoying a revival in our time. In particular, the inheritance of certain traits in mammals and yeast has been attributed very recently to a kind of "mutable" protein called the prion, and the notion that a defining component of some DNA-based genes might be proteinaceous is meeting with less resistance. It is a very exciting time!

We come now to our fourth and final example, which addresses your incredulity regarding the simplicity of DNA, that hereditary information can be determined by only four nitrogenous bases. Again, we apologize for our oversight. In fact, one can find over a dozen bases in addition to G, A, T, and C. These bases resemble the standard four bases but can have substituents that range from modest methyl groups to the more bulky polyamines, amino acids, and sugars. They can be incorporated during replication of the DNA or can result from modification of a base after its incorporation into the DNA polymer. The majority are found in phages, including the phage of Hershey and Chase where they replace 100% of the cytosine residues. However, several are also found in more complex organisms, including plants and animals. Will these figures have an impact on Chargaff's equivalence rule? The answer is that while the existence of modified bases will be known as early as the 1940's, these bases will not figure prominently in the studies of that time because, overall, they will be found to constitute only a minor fraction of DNA. You will be pleased to know, however, that by our time there will be a heightened interest in the "unusual" bases and a growing belief that DNA modification is a potent form of gene regulation.

These, then, are our four examples of instances in history when pursuit of the more promising route may have influenced the balance between focus and breadth. That is, in contrasting Mendel's peas with Mendel's Hieracium, Morgan's gene theory with Bateson and Pellew's paramutation, the Hershey-Chase experiment with the role of RNA and protein in heredity, and the focus on four nitrogenous bases with the discovery of many more, we wonder whether the push to find universal themes of heredity resulted in an underappreciation of the exception. Ultimately, this underappreciation may have played a role in what you have found to be our troublesome focus on DNA and our arguably constrained definitions of "gene," "genetics," and "epigenetics".

Moving on, we would like now to address specifically your interest in the etymology of "epigenetics". As you have alluded, "epigenetics" derives its origin from "epigenesis," which in your time as well as ours refers to the proposal that the complexity of an organism arises, unfolds, or develops from an initially undifferentiated entity and not, as suggested by the theory of preformation, from a miniature differentiated likeness found in the germ cell of that organism. How, then, will "epigenetics" come to be defined as changes in gene function that are heritable and that do not entail a change in DNA sequence? Donning our cloak of amateur historians we have found the following.

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. 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. The following excerpt is long but beautifully clear:

"Thus genetics has to observe the *phenotypes* (his italics), the adult characteristics of animals, in order to reach conclusions about the *genotypes* (his italics), the hereditary constitutions which are its basic subject-matter.

"For the purposes of a study of inheritance, the relation between phenotypes and genotypes can be left comparatively uninvestigated; we need merely to assume that changes in the genotype produce correlated changes in the adult phenotype, but the mechanism of this correlation need not concern us. Yet this question is, from a wider biological point of view, of crucial importance, since it is the kernel of the whole problem of development. Many geneticists have recognized this and attempted to discover the processes involved in the mechanism by which the genes of the genotype bring about phenotypic effects. The first step in such an enterprise is - or rather should be, since it is often omitted by those with an undue respect for the powers of reason - to describe what can be seen of the developmental processes. For inquiries of this kind, the word 'phenogenetics' was coined by Haecker (with reference given here to V. Haecker, 'Entwicklungsgeschichtliche Eigenschaftsanalyse,' *Phaenogenetik*, Jena.) The second and more important part of the task is to discover the causal mechanisms at work, and to relate them as far as possible to what experimental embryology has already revealed of the mechanics of development. We might use the name 'epigenetics' for such studies, thus emphasizing their relation to the concepts, so strongly favourable to the classical theory of epigenesis, which have been reached by the experimental embryologists. We certainly need to remember that between genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes. It is convenient to have a name for this complex: 'epigenotype' seems suitable (with reference given here to Waddington, 'Pupal Contraction as an Epigenetic Crisis in *Drosophila*,' *Proc. Zool. Soc. Lond*. (in press)]" (Waddington 1942, pages 18-19).

That Waddington is referring in his paper to the action of genes is clear from a later paragraph that states, "...the genotype is in continual and unremitting control of every phase of development. Genes are not interlopers, which intrude from time to time to upset the orderly course of a process which is essentially independent of them; on the contrary, there are no developmental events which they do not regulate and guide" (Waddington 1942, page 20). Thus, after more than two centuries of remaining relatively aloof from physical basis, epigenesis will find sure footing in the concept of the gene.

Waddington's definition of "epigenetics" will appear two years prior to the 1944 publication by Avery, MacLeod, and McCarty and therefore, while it will refer to the role of genes in epigenetics, it will not mention DNA. Nevertheless, by virtue of its focus on genes, its connection with DNA will be obvious when the role of DNA in heredity becomes accepted. Excepting a more explicit association with DNA, Waddington's definition will remain intact for several decades. In 1987, Robin Holliday, renowned by this time for his studies of the molecular mechanism by which chromosomes physically recombine, 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, a term first introduced by Waddington [with reference given here to Waddington, *Symp. Soc. Exp. Biol.* 7,186 (1953); *Principles of Embryology*]. Thus, epigenetic switches turn particular genes on or off during the developmental process, producing either transient changes in gene activity or a permanent pattern of activities" (Holliday 1987, page 163).

Seven years later, Holliday will again consider epigenetics. This time, however, he will develop the idea of epigenetics beyond Waddington's original definition. He will begin with, "The key feature is the unfolding of the genetic programme, which ultimately depends on the activation or inactivation of specific genes, or the interactions between genes and the products of genes" (Holliday 1994, page 453) and then suggest two variations of this definition with the intention of integrating some intriguing observations of gene function. The point we wish to emphasize is that these two variations will incorporate two new concepts to our understanding of epigenetics.

First, Holliday will point out that changes in gene expression occur not only during development but also during the adult stage of an organism. We believe that it is with this thought in mind that he will propose his first variation, a definition of epigenetics that "is not restricted to development, but to organisms that have several or many types of differentiated cells" (Holliday 1994, page 453). 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" (Holliday 1994, page 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, as seen in the production of genes coding for immunoglobulins. It could also include the alternative splicing of pre-mRNA transcripts to produce protein *isoforms*, which can be cell type specific" (Holliday 1994, page 453). (Immunoglobulins are proteins that mediate the ability of organisms to fight infection, and mRNA transcripts are RNA products of genes.)

This new definition will also clearly raise a second issue, which is the notion of inheritance. He will note that as changes in gene activity can be inherited through cell division, the "stable mitotic inheritance of given patterns of gene activity is a key feature of epigenetic controls" (Holliday 1994, page 453). How is this inheritance effected? 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. (It's true. DNA will prove to be quite the dynamic molecule!) Holliday 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, which brings the role of non-DNA elements into the limelight. He proposes a "supplementary definition of epigenetics to include transmission of information from one generation to the next, other than the DNA sequence itself" (Holliday 1994, page 454), in other words, "Nuclear inheritance which is not based on differences in DNA sequence" (Holliday 1994, page 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. We hope that it can begin to account for our current use of "epigenetics," especially when considered in light of the central position that DNA will assume in our interpretation of the gene. However, should you remain convinced that our focus on DNA is excessive, we urge you to seek consolation in, ironically, the definition of "epigenetics" itself. 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. Your flower, then, may yet be recognized for all its beauty.

Wishing you well and enjoying better weather, we remain eager to know your thoughts and more of your times.

Sincerely yours,
C.-t. Wu and J. Morris
December 1, 2000

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

Hieracium, the hawkweed? Of Nägeli's work on Hieracium, I have heard, but nothing in this regard with respect to Mendel! Your letter did, nonetheless, send me to my cold house where I found among our collections some three score or more seeds representing three varieties of Hieracium (one purported to be a wild form harvested from, by happy coincidence, the outskirts of Brno) and four of Pisum. These seeds lie now before me and, therefore, you as well as I should thank Fortune for the bitter cold of this winter. You see, by promising to endure for weeks to come, this ghastly weather keeps me from my gardens and leaves me no recourse but to apply the intervening time to questioning the wisdom of planting the seeds and learning what I should not know. Thus far, I have spoken to no one of our correspondence, though there is little doubt that common knowledge of our exchanges would lead to no more than their being dismissed as a dreamer's folly. On the other hand, to plant seeds that should otherwise lay dormant, and from these seeds produce progeny that challenge the Laws of Mendel - this could alter the course of history. Great has been my temptation, but an evening and a morning's pondering has made it clear that temperance in this instance must win the upper hand. Beyond my cantankerous objections, I remain in awe of what is forthcoming; though I trespass through time and torment you with questions, I cannot now think to change the terrain between us. If prominence of model organisms, a singular focus on DNA, and belief in the universality of hereditary laws are responsible, even if only in part, for the progress of this new century, then so be it. I will not tamper. Are you in disbelief over my agreeable change of heart? I will confide, then, that my good nature derives from the consolation which you offered and which has been heartily embraced. That the oddities and exceptions of the ensuing decades will not be altogether lost and even resurface in your time to some applause, well, such news is sufficient to appease this Nuisance from your past. I am content to know that while the Law and Rule will serve us well, so will the Renegade.

Regarding the etymology of "epigenetics," it is here you will find once more my more familiar self! While I followed your progression from one tier of interpretation to the next (even succumbing with reluctance when between Waddington and Holliday slipped in the gene and, by this turn, the concept of development was cast aside), 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? From my distant point of view, your final definition expresses but half the intention of Holliday and, in this way, is but a sorry substitute.

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. While preservation of gene state through cell division seems as reasonable and expected as it is implicit in the process of development, I fail to understand why, in defining Epigenetics, one must at all consider Inheritance from one individual to its progeny. Then, beyond confusion is my apprehension that, by their joining, Genetics and Epigenetics will each be diminished. 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? And to what advantage, I cannot see. Or, is your intention that Epigenetics, by its marriage to Inheritance, is a sort of Genetics? This too, would not seem a proper conclusion. That Epigenetics, once distinct from Inheritance and referring to "epigenesis" and the remarkable events by which genotype brings about form, will by your time be considered subordinate to Genetics, is an outcome most unbecoming.

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. If odd, I would agree. But if disturbing, I would entreat you to accept my deepest apologies for, however ill-tempered or ungrateful I may seem, my appreciation for all that you have extended to me is great. That I should find resolution in ancient meanings is in no small degree even a surprise to me. 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. May this letter find you in good health.

Respectfully yours,
M. Bacon
March 29, 1910

P.S. Whatever will become of William Bateson? Will he find reconciliation with the chromosome theory?

Dear M. Bacon,

Your points are well taken and by no stretch of the imagination have we found your input disturbing. In fact, your cautionary comments have been very helpful as we prepare for this year's course on epigenetics and are, again, struggling with the introductory statements. Regarding the "sorry substitute," we would guess that Holliday would more than readily agree with you for he, himself, warned in his 1994 paper against simplifying "epigenetics" to just one of his two definitions: "Both definitions are incomplete..." (Holliday 1994, page 454). 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, only one of which have we discussed in our letters? 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. For example, would a particular change in gene expression be both epigenetic and not if in one circumstance it is inherited, but in another it is not? Rather, if we understand you correctly, epigenetics should concern the discrete events of or affecting gene activity or capacity (which altogether would chart the course of development or differentiation), but refrain from taking into account heritability at a later time. Inheritance, on the other hand, should concern the process by which traits are transmitted, but not be limited by mechanism or defined by the function, history, potential, or chemistry of the elements responsible for the traits, these elements being, and fully defining, the genes. This interpretation *is* enticingly simple, 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: "But the most misunderstanding arises, I venture to think, from a confusion of the problem concerned with the sorting out of the hereditary materials (the genes) [Morgan's parenthetical statement] to the eggs and sperms, with the problems concerning the subsequent action of these genes in the development of the embryo" (Morgan 1917, page 514). Thank you for being the instigation for us to go back and find this clarifying paragraph.

Which brings us to William Bateson who, by his very effective advocacy of Mendel, will be responsible in part for Morgan's conversion to Mendelism, but who will also stand for many years in opposition to Morgan regarding the chromosome theory of inheritance. In December of 1921, however, Bateson will visit Morgan's laboratory at Columbia University in the United States and, a few weeks later, will come to accept, reluctantly, the chromosome theory. He will maintain, with Beatrice Bateson, an active research group in England as well as travel widely, doing more than his part to introduce the Laws of Mendel and the discipline of genetics to other nations. At the same time, Bateson will also be a champion of the exception, of the need to exercise both caution and open-mindedness in the face of doctrine. We leave you with a quotation from Bateson, taken from his 1926 paper on "Segregation". Although this paper can be criticized, and was criticized at the time, for its defense of a proposal called the Presence-and-Absence hypothesis and for its stand against the universality of the chromosome theory, it carries a message, embodied in the quotation, that is greater than the details it argues. We believe that it may be to your liking as it seems to speak to your Renegades and 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" (Bateson 1926, page 201).

Sincerely,
C.-t. Wu and J. Morris
January 18, 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
May 16, 1910

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