Sci & Educ (2013) 22:325–344
DOI 10.1007/s11191-011-9367-y

On Gene Concepts and Teaching Genetics: Episodes from Classical Genetics

Richard M. Burian

Published online: 24 May 2011

Abstract This paper addresses the teaching of advanced high school courses or undergraduate courses for non-biology majors about genetics or history of genetics. It will probably be difficult to take the approach described here in a high school science course, although the general approach could help improve such courses. It would be ideal for a college course in history of genetics or a course designed to teach non-science majors how science works or the rudiments of the genetics in a way that will help them as citizens. The approach aims to teach the processes of discovery, correction, and validation by utilizing illustrative episodes from the history of genetics. The episodes are treated in way that should foster understanding of basic questions about genes, the sorts of techniques used to answer questions about the constitution and structure of genes, how they function, and what they determine, and some of the major biological disagreements that arose in dealing with these questions. The material covered here could be connected to social and political issues raised by genetics, but these connections are not surveyed here. As it is, to cover this much territory, the article is limited to four major episodes from Mendel's paper to the beginning of World War II. A sequel will deal with the molecularization of genetics and with molecular gene concepts through the Human Genome Project.

1 Introduction

I am not well acquainted with the literature in education or education and science, and I have never taught genetics. So I hesitate to make strong recommendations about the structure, content, and teaching methodology of courses in this domain. Nonetheless, I have studied and taught the history of genetics and gene concepts off and on for 30 years (Burian 1981–1982, 1982, 1987, 1993a, b, 1997, 2000, 2004, 2005a, b, 2007; Burian et al. 1988, 1991; Burian and Zallen 2009; Gayon and Burian 1999; O'Malley et al. 2010; Thieffry and Burian 1996), have taught college and post-graduate courses in philosophy of biology, and have thought rather hard about the problem of teaching students the

R. M. Burian (✉)
Department of Philosophy, Virginia Tech, Blacksburg, VA 24060, USA
e-mail: rmburian@vt.edu

complications encountered in the history of genetics and in current genetic research. With the modesty appropriate to someone with limited experience in the trenches, I nonetheless put forward a strong viewpoint that diverges in some ways from what I found in this journal about how best to introduce students at the high school and early college levels to the complications of genetics. There is, of course, no one right way to teach such a course—and a great deal depends on the specific purpose(s) of the course and the level and previous preparation of the students. I have in mind here primarily students who (in general) are not planning to go on to careers in biology or science, but whose lives—and whose societies—will be greatly affected by developments in genetics in the next decades. I assume that these students will probably face issues (whether personally or in evaluating policy options that are politically salient) that call for some understanding of new scientific findings and that the relevant science will continue to change at a rapid pace. Accordingly, I hold that it is less valuable to teach the specifics of a variety of techniques, theories, or conceptual models, and more important to understand the processes of investigation and the fundamental issues that are posed by genetic sciences. This paper develops an approach along these lines, suited for unusual courses in one of the two last years of high school (courses that don't seek to teach the latest scientific details or techniques) or for introductory courses in history of genetics or genetics for non-scientists in college.

My approach differs somewhat from those presented in two recent papers in this journal (Gericke and Hagberg 2007; Smith and Adkison 2010). These papers provide enormously useful models of the conceptual schemes employed in thinking about genes at different stages of the history of genetics. (In each case, a few details call for improvement, a task for which I have no room here). But the models, I think, do not provide an adequate sense of how the discovery process works, nor of the continuities that are prevalent throughout the history of genetics. I recommend a different approach that emphasizes the processes of discovery (including some attention to the technical modalities available to researchers) employed in studying the material, structure, and functions of genes. How are new discoveries made, verified, and corrected? What are the strengths and weaknesses of claims made when the instruments employed are new and the theories only partly tested? Where do conflicting claims come from and how are they evaluated? Rather than concentrating on the details of the models, which is likely to 'freeze' the state of knowledge (or of the relevant theories), I suggest concentrating on the basic questions that motivate research, the means that scientists employ for improving knowledge, and the strengths and fragilities of the processes used to correct and refine new knowledge and applications of that knowledge. I also place (I think) greater emphasis on the changing experimental tools that facilitated many of the major changes in genetic research, genetic theories, and gene concepts. This approach should help students balance respect for the depth of knowledge and security of findings that undergird the forefront advances of science with skepticism about exaggerated claims about what science can accomplish. If successful, it should provide them with an understanding of science as open-ended, incomplete, but developing dynamically. It should also provide them with useful background when they face real-life questions requiring them to rely on—or be skeptical of—specific scientific claims based on genetics and allied sciences.

Considerations about what students are likely to retain a year or two after taking a course like the ones we are considering favor a process-based approach. As I understand it, students are less likely to remember the details and complications of intricate models and more likely to remember the kinds of processes that go into correcting open concepts like that of the gene and strong, straightforward claims like the claim that genes are like beads on a string, or that protein-encoding genes are often split into coding and non-coding

sections (exons and introns). Indeed, if a simplified reconstruction of the discovery, correction,[1] and verification processes enables students to arrive at improvements of simple models and to construct improved models on the basis of summaries of 'new' evidence, they will have gained some appreciation not only of gene concepts, but also of scientific processes, a sense that they are likely to retain longer than the details of specific accounts of the gene. But to achieve this, students must be actively involved in the correction process rather than presented with a scheme encompassing the results of that process. By concentrating on the most basic questions that geneticists sought to answer, on ways in which the evidential basis for answering those questions changed over time, and on how the tools and instrumentalities for producing relevant evidence changed over time, a process-focused course can help students gain better understanding of the power and the limits of concepts of the gene and the ways in which scientists go about improving their concepts and correcting their errors. I suggest that a process-based approach will do better than one based on intense attention to the details of specific models of genes and of gene action.

This approach shares the view, common to the authors of the papers mentioned above, that it is important to introduce students to the complications of current genetics by following the development of gene concepts. An emphasis on the processes by which corrections and extensions of fundamental claims and concepts were made should help students to understand the underlying conceptual continuities involved, to understand how evidence leads to revaluation of even rather fundamental claims, and to develop an appropriate mixture of skepticism and respect when they encounter claims that genes are responsible for various traits of plants and animals, including humans. For the majority of students it is especially important to gain some sense of what can sensibly be attributed to genetic determination and what to make of claims that some individual(s) have a genetic condition or that genetically modified crops will reduce the amount of pesticide required without harming the environment or humans. Detailed models of the gene and of gene function will not generally help them in such matters, but some knowledge of the sources of challenges to such claims and of how scientists go about evaluating them may be of considerable help.

In order to illustrate the approach I recommend I will present four vignettes in this paper and more in the sequel. The first vignette concerns Mendel's work (which belongs to the prehistory rather than the history of genetics), the second covers the first decade after the 'rediscovery' of Mendel, and the final two concern serious challenges to the gene theory in the 1930 s. With each episode I present some comments on how to extract fundamental points that students are likely to retain. The sequel will continue in similar style with developments during the still-ongoing molecularization of genetics, starting with the Watson–Crick model of the gene.

2 Mendel's Research in Hybridization: Prehistory of Genetics

Although Mendel is usually considered a founder of genetics, he was not known for a theory of heredity in the nineteenth century, and was not credited with having one until 35 years after he published his famous experiments (Mendel 1865, 1966). His experiments

[1] In the concluding section of Bachelard (1934/1999), Gaston Bachelard wrote that we think scientific truth as the historical rectification of a long [train of] error. Thanks to an anonymous referee for suggesting the relevance of Bachelard to this point.

were not designed to study heredity as such, but to provide a system for producing new kinds of plants by making hybrids that would yield stable true-breeding varieties or species with new combinations of traits (Corcos and Monaghan 1992; Müller-Wille and Orel 2007; Olby 1979; reprinted in Olby 1985). The experiments involved the crossing of pea plants differing in one, two, three, or even four traits; they yielded a "law for peas" (i.e., Mendel's laws as exemplified in peas) without producing an explicit theory of heredity. Mendel, of course, was confident that his laws applied to other plants too, but not that they applied to animals or to all plants, as his subsequent aborted work on hawkweeds (*Hieracium*) shows (Mendel 1869; translated as Mendel 1909). The empirical laws worked like this: when two true-breeding strains of peas that differ in one well-chosen trait (say, flower color or plant height) are crossed, the first generation hybrids all exhibit the 'dominant' trait, in the examples, purple flowers (which are dominant) or white flowers, 6–7 feet tall (which is dominant) or 2–4 feet tall (i.e., short). The first generation hybrids from plants differing only in flower color all have purple flowers; if these hybrids are self-fertilized, the statistical average of their offspring will be very close to one quarter true-breeding dominants (i.e., will have purple flowers, but when self-fertilized will breed true), one quarter true-breeding recessives (i.e., true-breeding with white flowers), and one half hybrids, (purple-flowered, but behaving like the first generation hybrids when self-fertilized).

If one constructs a double hybrid, e.g., by crossing a true breeding tall and white-flowered plant with a true-breeding short and purple-flowered plant, and then self-fertilizes the first generation hybrids (which will all be tall and purple flowered), the two paired traits turn out to be inherited independently. A reasonable exercise for students is to work out what this means. (The result, of course, is that there are 9 distinct varieties present in the following proportions—1 pure tall and pure purple-flowered: 1 pure tall and pure white-flowered: 1 pure short and pure purple-flowered: 1 pure short and pure white-flowered: 2 pure tall and hybrid purple-flowered: 2 pure short and hybrid purple-flowered: 2 hybrid tall and pure purple-flowered: 2 hybrid tall and pure white-flowered: 4 hybrid tall and hybrid purple-flowered). Thus, starting from true pure-breeding stocks, Mendel could obtain four pure-breeding stocks, two of which had novel combinations of traits and bred true from then on.

Mendel tried this sort of thing out with many combinations from 14 stocks (better put: 7 pairs of stocks with each pair differing markedly in only one character), carefully chosen in preliminary experiments to breed true. His results were similar to those sketched above in every case except, of course, that with repeated crosses he could get more complex crosses and could produce any of the 2^7 [=128] trait combinations feasible from the seven pairs by hybridizing plants with a given trait with other plants with different traits in the experimental group. The statistical methods he employed were new to botanists and hybridizers, especially as applied to three or four generations in the more complex crosses, and found no acceptance among the few people who read Mendel's paper in the next 30 years or so.

According to the usual interpretation of Mendel's paper, disputed by some who think of him as focusing on hybridization (Kampourakis 2012; Olby 1979, 1985), he devised a theory of heredity to explain these rather complex results. In any case, Mendel's theory was later transformed into the Mendelian theory of heredity. Interpreted as such, it worked as follows: A hybrid plant (for one trait) carries two "factors"—one for one variant of the trait, the other for the other. The factors assort at random to the germ cells. That is, half of the pollen grains (which play the role of sperm) get one factor, half the other, and half of the ovules (egg cells) get one factor, half the other. Thus, the first generation hybrids from true-breeding 'opposite' parents each would have one copy of each of the two factors for

the trait in question. Given dominance, they would all exhibit the trait variant of the parent with the dominant factor. On the assumptions that the pollen grains meet the ovules at random in fertilization and that all the offspring are equally likely to survive, self-fertilization or crossing of first generation hybrids should, on average, yield crosses with the following constitutions: ¼ of the fertilized eggs should have the recessive factor and have been fertilized by a sperm with the recessive factor; ¼ would have the recessive factor and meet a sperm with the dominant factor; ¼ of the eggs should have the dominant factor and meet a sperm with the recessive factor, and ¼ should have the dominant factor and meet a sperm with the dominant factor. Result: ¼ of the fertilized eggs would have the recessive trait and yield plants that breed true, ¼ would have the dominant trait and yield plants that breed true, and ½ would exhibit the dominant trait but be hybrids. More complicated calculations yielded the correct ratios for the crosses of double (and even triple) hybrids.[2]

It is useful to pay attention to the dramatic difference between the reception of Mendel's theory 1865–1900 and its reception after 1900. Salient issues include the revised interests of biologists, who, in the intervening time, had moved the problem of heredity to center stage in part as a consequence of the new interest in evolution unleashed by Darwin and the subsequent controversies over evolution. Some of them also became preoccupied with the use of experiments to make their science into a 'hard' science like physics. Furthermore, the development of cytology suggested looking inside cells for mechanisms that affected development and inheritance, and to make these into experimental topics (cf. the development of experimental embryology). In addition, there had been significant development of statistical methods, and, in England, the attempt by Darwin's second cousin, Francis Galton, to apply those methods to understand how they could illuminate human heredity. Galton devised the term 'eugenics' for a proposed science of improving the human race by good breeding as well as sound hygiene and education.[3] Thus the period in which Mendel was ignored may have been the result not only of the specialized project of improving plant breeds in which he was engaged, not only because he used somewhat esoteric statistical methods that required tedious and careful experiments over a several years, and not only because he published in a relatively obscure journal, but also because there was not the broad readership interested in such exact experiments or in the topic of heredity as there was by 1900. Cultural changes and the changes in the standards of scientific work were critical for the changed reception that his work received in 1900 as compared with when he published.

3 The Earliest Days of Genetics

Kostas Kampourakis's article in this volume sets the historical background in nineteenth century theories of heredity that preceded genetics (Kampourakis 2012). Mendel's theory (treated as a theory of heredity) was far from the only theory of heredity at the time;

[2] By outlining the Mendelian laws this way, it is possible to set up a suitable exercise for students to try out the calculations for themselves for dihybrid and even trihybrid cases. Also, note that Mendel's language was ambiguous about whether true-breeding plants had one factor or two, but his symbolism suggests that he may have thought that they only carried one factor, not two, but that sperm and egg each got one copy of that factor. For more on this see Müller-Wille and Orel (2007), Olby (1979, 1985) *Origins of Mendelism.* Chicago: University of Chicago Press. Mendel claimed that there are as many factors as there are segregating traits that behaved in accordance with his laws.

[3] The term 'eugenics' (which means 'good breeding') was invented by Francis Galton. He introduced the idea in (Galton 1865, 1869) and the term in (Galton 1883).

indeed, many other major biologists, including Darwin, Brooks, Galton, Nägeli, de Vries, and Weismann, had theories of heredity in the nineteenth century. Furthermore, Mendel's theory was virtually unknown—only 16 pre-1900 references to his 1865 paper have been found in the literature from 1865 to 1900 (Olby 1985, appendix to chap. 5), none of them in major works and none of them with a clear account of what he had done. The 'rediscovery' of his work in 1900 was dramatic, with five very visible publications (two in French, three in German) by the people who first reported on his work in that year and a considerable flood in the next few years (Special Issue: 2000, Stern and Sherwood 1966). Furthermore, by then the context in which Mendel's work was considered was dramatically different, for the rediscovery followed the discovery of the 'dance of the chromosomes' in mitosis and meiosis, which, by 1900, had been described in considerable detail by microscopists. Since the 1880s, microscopists had the advantage of improved microscopes and enormously improved visibility of various parts of living cells thanks to the use of vital dyes that enabled previously-invisible features like chromosomes (the term means colored bodies) to be stained and visualized; during the 1890s breeders and hybridizers had done a good number of similar experiments and become familiar with the statistical techniques for following traits across several generations that Mendel had employed in 1865. In this new context Mendel's work quickly became famous and became the starting point for the new science of genetics that was institutionalized during the decade from 1905 to 1915.

Although the term 'gene' was not suggested for Mendel's 'factors' until 1909 (Johannsen 1909) and did not become fully standard until sometime between 1915 and 1920, by 1906 several different attempts to develop Mendel's theory as a framework for understanding heredity were already available. By 1906, it was clear that Mendelian heredity was found in several species of plants and animals, that at least seven groups of fundamental questions had already been staked out, and that the new science was committed to answer them. (For an earlier development of this claim, see Burian 2000.) In good part, the historical continuity of genetics as a discipline stems from its commitment to answer all of these questions, even when the answers seem (for a while, at least) to point in different directions (Burian 2000).

- Where are genes located? How many genes are there? How are genes duplicated (or self-duplicated) and transmitted across generations? (This group of questions, as we will see, became the focus of (chromosomal) transmission genetics.)
- How are they changed, mutated, or varied so that there are enough different sorts of genes and enough variants of particular genes to account for all the traits that they determine or affect?
- What is the inner structure or organization of genes? Of what are they made? How are they individuated?
- What metabolic processes are involved in their production? What metabolic processes do they enter into or control? (In short: what is the physiology of genes?)
- How do they act, e.g., to influence the development of the organism, to yield traits, to interact with other genes to yield complex traits? (This and the preceding group of questions became the domain of a subdiscipline, "physiological genetics," by the end of the 1920s.)
- Given that they do these things, how do genes (or does genetic change) influence evolution? (This question became the focus of population and evolutionary genetics.)
- Or are genes, perhaps, just a convenient shorthand, an instrument for calculating the likelihoods of different that traits will be passed on across generations in different circumstances rather than independent material entities or realities?

Next I illustrate some of the ideas that were already in the literature in the years 1900–1910 to reinforce the fundamental and obvious character of these questions.

(1) Mendel already offered a preliminary idea about the number of genes: there are as many genes as there are independent traits that exhibit the sorts of patterns of inheritance that the seven trait-pairs of peas exhibited in his experiments. And the factors (genes) must be present in single copies in the germ cells (sperm and eggs, pollen and ovules). (Mendel was not clear whether there was just one factor or two copies of that factor (one from the egg, one from the sperm) in the somatic cells of non-hybrid organisms.)

(2) By 1902 two different experimenters (Boveri 1902; translated as Boveri 1968; Sutton 1902) suggested that factors would be part of, or carried on, chromosomes and that the behavior of meiosis in sexual organisms would explain how the two copies of a gene (whether alike or different) would be segregated separately into germ cells so that those cells would have only one copy of a gene, but somatic cells would have two copies, one on a chromosome from the mother, the other on a chromosome from the father (Sutton 1902, 1903).

(3) These last suggestions, controversial at the time because the continuity of the chromosomes through the entire cell cycle was not yet definitively established, provided an initial answer about how factors are duplicated (they are duplicated by the process of chromosome duplication) and transmitted across generations. One problem, much discussed, was that there must be a huge number of factors on each chromosome, because there are so many more discretely inherited traits than there are chromosomes. Indeed, the chromosomal hypothesis was generally rejected for almost a decade, because chromosomes are duplicated as wholes and the number of chromosomes was far smaller than the number of segregating traits, so it seemed most unlikely that there was any way for chromosomes to carry enough factors to account for all the different independent traits. A common argument (put forward by T.H. Morgan among many others) was that once one was allowed to assign as many factors as needed, one could freely invent an explanation for any outcome of a breeding experiment, with no cross on the existence of the supposed factors involved (Morgan 1910a). That Morgan emphasized this objection is somewhat ironic because, after 1910, it was Morgan and his students who showed how to tell where different factors are located on chromosomes and who began to count genes using the criteria for locating them on chromosomes, thus resolving the puzzle that Morgan had thought, before 1910, counted as a key argument against the Mendelian theory.

(4) One early answer as to how genes act was proposed by Lucien Cuénot (Carlson 1966, Cuénot 1903); it was that some factors, at least, are, or somehow control, enzymes—e.g., that in the formation of hair pigments in mice, different genes control an enzyme required for forming pigments (chromogen) and a series of enzymes needed to make different pigments or components of pigments.

(5) During the decade after 1906, William Bateson (who served as "Mendel's bulldog" in England and first introduced the term 'genetics' publicly in 1906) argued against the idea that genes could be particles on (or incorporated into) chromosomes because genes had to control the development of the form of organisms. One argument for this view was that there are often discrete steps between different forms. Thus, there are no half-petals or sepals, etc. in plants—the number of petals change in whole number steps in evolution and under mutation—and no half vertebrae in vertebrates—they,

too change in whole number steps.[4] He argued that if genes were to dictate form (as they must!) they could not be inert particles, but had to have dynamic features like those of a standing wave on a tympani head. Such waves have complex forms, but also change in stepwise fashion, so that there are six, seven, eight or nine (etc.) whole 'waves' within a confined space. (That is, as one can see more easily on violin strings, the waves always end at a node, never between nodes.) Since there always is a whole number of wave-lengths for each frequency of vibration in a standing wave, such a 'vibratory theory' can (in principle) explain this aspect of the creation of form. Bateson claimed that particles (which, as such, he considered to be inert) could not dictate such a result, but that stable harmonic resonances could, so he suggested (without ever introducing a proper theory) that factors (genes) must be some sort of stable harmonic resonances. (See, for example, the discussion of segmentation and regeneration in chapter III of Bateson 1913, reviewed in Burian 1982, see also Newman 2007).

The moral that I want to draw from this attention to the prehistory and the earliest days of genetics is that most of the fundamental questions still open today were being asked in rudimentary form from the very beginning of the discipline. These questions provide considerable continuity through all the complexities that have arisen since and allow one to pose the major issues that still remain open as extensions of familiar questions that continue to call for reworking and refinement in relatively simple ways. Scientists returned time and again to each of the questions as they developed new tools that might improve the provisional answers that had been given to them. And as new experimental tools provided new (potential) answers to some of the questions, the revised view of the constitution, location, or action of genes fed back onto the work on the other questions, setting off a cascade of further revisions and the search for better experimental answers to the discrepancies between the various positions that scientists supported.

Similar points apply to some of the socially relevant issues raised by genetics—starting with eugenics, which arose out of theories of 'hard' heredity (which, of course, include Mendelian genetics). The eugenics movement was most prominent in the countries where Mendelian genetics was most prominent (Adams 1990). One reason for this is that eugenics was fostered by major geneticists. For example, Charles Davenport in the US, the long-term director of the Cold Spring Harbor Laboratory, also directed the Eugenics Record Office, which was central to the formation of the model laws in the U.S. that excluded immigrants from southern and eastern Europe and served as models for the Nazi eugenic laws (Kühl 1994); see also http://www.eugenicsarchive.org/eugenics/). This, however, is a topic for another paper.

Here it is important to pursue the processes by which the fundamental questions listed above became more sophisticated and by which various attempts to answer them and various conceptions of genes were corrected and improved. These processes are still ongoing—and the core of my argument is that the processes deployed in answering a relatively small number of fundamental questions are far more important to teach to young people entering civil as well as professional lives than the details of the particular models that were prevalent at various times and are prevalent today.

[4] Bateson provided many other examples to show that these examples are typical of a large class of cases affecting the form of organisms.

4 Early Difficulties and Early Partial Resolution of Some of Our Questions

As indicated above, several theories of heredity were in play before the 'rediscovery' of Mendel. These theories were, in a way, too ambitious, and, in another way, not clear enough. Too ambitious because they attempted to solve simultaneously problems about the development of embryos, about evolution, about medical problems caused by inheritance, and about general features of (supposed) human (and plant and animal) races. Not clear enough, because what later became separated as concepts of evolution, embryological development, and heredity where complexly intertwined and not clearly separated (Kampourakis 2012). One consequence of this is that the proponents of several rather different theories tried to incorporate Mendel's findings into their own theories. The proponents of August Weismann's theory of embryology and evolution for example, claimed that Mendel's factors were the same as the *Anlagen* (primordia of organs and characters) that Weismann had identified with a complex theory of the determinants of traits and organs contained on chromosomes—determinants that were parceled out to different cells from the nucleus in the course of development so that (for example) skin cells had only skin determinants, kidney cells had only kidney-cell determinants, etc. Hugo de Vries, one of the rediscoverers, claimed that Mendel's factors were what he called 'pangenes', a term he had revised from Darwin for determiners of cellular traits and composition of organs (De Vries 1889; translated as De Vries 1910). Darwin had thought that pangenes (he actually called them 'gemmules') could be sent from all sorts of cells to the gonads, a doctrine that Galton, who conducted experiments to show that they are not circulated through blood (Galton 1871a, b), denied.

So did de Vries; he argued that pangenes are not transported between cells, but are present in the nuclei of germ cells as soon as they are formed. He supported various revisions of Weismann's views in seeking to explain how pangenes related to the characters of cells and organisms and emphasized the need for variation in the pangenes in order to achieve different traits and, ultimately, different species. Later he transformed his claims about variation in pangenes to make it the basis for a theory more explicitly about evolution than Mendel's, known as Mutationism (De Vries 1901, translated as De Vries 1909–1910). De Vries's mutations, unlike what ultimately resulted from the study of Mendelian mutations, were supposed to cause discrete steps large enough to produce new species in one step and be a cause of evolutionary change independent of processes like Darwinian selection. The addition of discrete phenotypic units, as wholes, in evolution reinforced Bateson (who stayed loyal to his version of Mendel's theory) in his view that that factors could not be 'inert particles', a claim for which he provided several arguments. Among these were his argument that whole parts (such as a feather, petal, or vertebra) could not be added or subtracted in stages by gradual selection and that if factors were mere particles one could not understand how such parts could be added as wholes. Indeed, he claimed, discrete, stepwise inheritance meant that selection could not work by small gradual changes in the way that Darwinians thought to be the basis of evolution, at least in England at the time (Provine 1971). Thus Mendelian factors were fundamental for the understanding of evolution and, according to Bateson, required steps larger than most Darwinians had anticipated, putting mutational change beyond the immediate control of selection and requiring a mechanism for adding and subtracting entire parts or segments as wholes.

The quarrels among these and other views grew so intense that, when Wilhelm Johannsen offered the term 'gene' to stand for Mendelian factors, he did so to empty the term of all this other content and make it what some philosophers call an "atheoretical"

term (i.e., in this context, uncommitted to any claims about the internal structure or content of genes): genes were supposed to be the things or process, whatever they might be (no commitments to the answer implied), that cause particular Mendelian regularities:

> The word 'gene' is completely free from any hypotheses; it expresses only the evident fact that… many characteristics of the organism are specified in the gametes by means of special conditions, foundations, and determiners which are present in unique, separate, and thereby independent ways—in short, precisely what we wish to call genes (Johannsen 1909, transl. in Carlson 1966, pp. 20, 22)".).

We have here an attempt to separate a "functional" gene concept—the concept of something that performs some job—from a "structural" gene concept—something that is identified by its intrinsic structure or material content. In its pure form, a functional concept can be separated from any commitments about the underlying structures or processes that bring the function about.

However, from the earliest days of genetics forward, it was not possible to fully separate structure and function. Sometimes, for some purposes, one was better understood than the other, and would provide guidance about the other, sometimes, for some purposes, the structural and functional knowledge of genes would swap these roles, but there has always been—and continues to be—tension between them.[5] The fruitful, but difficult, tension between structural and functional criteria for identifying genes has proved to be one of the most important continuities in the history of genetics. We will follow that as a key thread throughout the rest of this paper.

5 The Establishment of the Chromosomal Theory by the Morgan School

Famously, the most developed branch (or program of research) of genetics from 1910 to 1940 was (chromosomal) transmission genetics. The work in question became a full-fledged research program when T. H. Morgan (and his students and colleagues) developed early findings into an experimental program employing Drosophila (a genus of fast-breeding fruit flies that are easy to raise in the laboratory) as an experimental organism (Allen 1978, Carlson 1974, Kohler 1994, Muller 1946, Sturtevant 1959).[6] A major advantage of the experimental species of Drosophila is that they have only four pairs of easily distinguishable chromosomes, one of which, the X (or sex) chromosome is carried in only one copy by males and in two copies by females. This means that an unusual variant of a gene carried on the X chromosome, if it has visible effects, is *always* visible if it is carried on males, but may not be visible (if it is recessive) if it is carried on females. Furthermore, if a male with a recessive gene on that chromosome is crossed with a female that does not carry the recessive gene, one-half of his grandsons will exhibit the same

[5] For an exemplary text comparing cytological (i.e., structural) knowledge of chromosomes and functional-genetic knowledge, and illustrating how each could be used to correct and improve the other, see (Darden 1991); for a recent anthology of historical and philosophical essays tracing these issues up to the beginnings of the human genome project see (Beurton et al. 2000).

[6] Garland Allen (Allen 1979) sets an important part of the background regarding the turn to experiment to resolve biological disputes and the way the shift toward experiment affected the development of both embryology and genetics. For a useful reworking of Allen's general views on these topics, see also a "Special Section on American Morphology at the Turn of the Century" in the *Journal of the History of Biology* (vol. 14, no. 1) edited by Jane Maienschein, Ronald Rainger, and Keith Benson, with contributions by each of the editors plus Garland Allen and Frederick B. Churchill. The topics covered there are more general than the title of the special section suggests.

variation, while none of his granddaughters (who will have inherited a 'normal' X chromosome from their mother) will inherit that variation.

This unusual "criss-cross" or (as Morgan called it) "sex-limited" pattern of inheritance is quite conspicuous, and was first discovered in 1910 with a sex-linked mutation that gave its male carriers white, rather than red, eyes (Morgan 1910b).[7] Within a year, Morgan and his students worked out a great many details about such inheritance. For example, by breeding females with X chromosomes homozygous for (i.e., both carrying) the recessive 'white' variant of the gene, they showed that they could produce white-eyed females. They also showed that there were several distinct factors (they still used that term) on the X chromosome, but that they were not all inherited independently (Morgan 1911a, b, c). Furthermore, there was a plausible mechanism (now called crossing over) that could explain how 'closely linked' genes could stay together more frequently than genes separated by a greater distance. The explanation was that during chromosome pairing in meiosis, paired chromosomes exchange short pieces (Morgan 1911d). By this point, Morgan was converted to the Mendelian theory—now he could tell how many factors he was dealing with and where they were located! By 1913, Alfred Sturtevant, one of Morgan's undergraduate students, showed that, on the assumption that the chromosome is linear, genes closer to each other will be inherited together more frequently than distant genes and that one could get a linear ordering of six of the known mutations on the X-chromosome by using the rates of crossing over between the alleles with visible effects to measure how far apart the factors in question were relative to each other (Sturtevant 1913). Indeed, application of this technique soon established that there are strong correlations between the visible cytological marks on chromosomes and the locations of mutations of alternative 'alleles' (alternative versions of a gene). These results were quickly generalized and applied to other (non-sex) chromosomes of drosophila and to many other animals and plants as well. The development of the transmission theory of genetics was very quick from this point forward, for one could correlate cytological and genetic changes and cross-check whether genetic and cytological predictions (where both were applicable) correlated with each other or not. Where they disagreed, detailed investigations almost always were able to resolve the conflict within the limits of experimental error in a way the increased reliance on, and reliability of, the chromosomal markers for the locations of genes (Darden 1991).[8]

By 1915, this and a raft of additional work had been codified into a textbook in which the transmission of genes across generations was explained, first, by the mechanisms of division and propagation of chromosomes and, second, by the localization of genes as very small segments or parts of chromosomes (Morgan et al. 1915). This textbook and the continuing work of the Morgan school (which included a lot of work to institutionalize and expand the practice and application of genetics in their style) established the orthodox

[7] Recall from point (3) in §3 that T. H. Morgan had been arguing against Mendelian theory as late as the middle of 1910. He had followed the Mendelian theory since the earliest days of the discovery, but argued that, in the absence of any cross-check on how many factors there are and where they are located, one could postulate any number of factors and then use them to predict any specific pattern of inheritance. Thus the discovery of the white-eyed fly, of criss-cross inheritance, and of the many other factors located on the X chromosome of drosophila convinced Morgan that this class of objections had been overcome and that Mendelian genetics (reinforced and developed in light of the experiments of his group and of many others) was both a practical and a well-supported theory. The literature on Morgan and the development of genetics is enormous, but some starting points are Allen (1978), Darden (1991), Gilbert (1978), Maienschein (1991), and Sturtevant (1959).

[8] The best technical history of this work is Carlson (1966, reprinted as Carlson 1989).

account of the 'nature' of the gene and of its duplication and transmission until after World War II. The main details of the chromosomal theory were in place and thoroughly supported by the early 1920s.

Note that the Morgan school's work provided (provisional, but strong) answers to some of the questions listed above, but not to others. They clearly answered the question of where genes are located (they have specific locations on various chromosomes). To be sure, Bateson, Johannsen, and several others contested that claim well into the 1920s, but the answers to how genes are transmitted across generations, the correlations between microscopically visible markings on chromosomes, and the claims about transmission of particular genes or alleles won over the vast majority of geneticists. Yet, the answers to the transmission and location questions did not yet deal with what genes are made of, how they are mutated, how they act to produce traits, or with their internal structure or organization. Worse yet, the resolution of microscopic images and biochemical analyses of chromosomes were unable to pin down *exact* locations of genes or to determine whether genes are separate molecules attached to chromosomes, parts of chromosomes, made of protein (a major component of chromosomes) or made of something else. Although it was known that nucleic acids (the distinction between RNA and DNA was still being worked out) are an important part of chromosomes, the best biochemical work on DNA in the 1930s suggested that it was a 'boring' molecule, consisting of repeats of a single sequence of the four nucleotides (e.g., ACGTACGTACGTACGT…) and thus that it could not produce the immense variety of states and conditions needed to dictate the construction of all the specific different molecules and parts of an organisms. Thus, although no one thought that the question had been resolved, those who accepted a materialist answer to "What is a gene?" were largely persuaded that genes are made of proteins.

It is important to recognize that the Morgan school and the chromosomal theory did not answer all the fundamental questions on our list of the questions that geneticists recognized early on as crucial to their discipline. There was little progress on *how* genes caused traits such as coat colors or eye colors, and even less progress on how they could cause the distributions of colors into coat color patterns or how genes could set up the differences between different kinds of cells within the organism (for all of them had exactly the same genes!) or the form (morphology) of organisms. No serious connection was established between the genetic constitution of organisms and their development (that is, how the genes dictated that an organism would turn out to be, say an elm tree, a cat, or a dog, or how genes could determine or cause the sequence of events in development, or, for example, the secondary sexual characters of an organism). The advocates of the chromosomal theory largely set these questions (including the biochemical composition of genes) aside, at least temporarily, or left them for other specialties within genetics to cope with.

6 Two Exemplary Problems in the 1930s

Efforts to pin down answers to the precise location, constitution, and physiology of genes ran into difficulties of various sorts. I illustrate two of them here, both presenting fundamental challenges to orthodox views. Within the Morgan school, there was vacillation about whether genes are separate material entities (pieces of chromosomes or particles carried on chromosomes) or calculational representations of the effects of microscopic changes in chromosome constitution with no safe interpretation in terms of the underlying entities, a position defended as late as 1954 (Stadler 1954). Morgan himself sometimes

claimed that the constitution of genes is not critical, vouchsafing only that that they are co-located with parts of chromosomes, but sometimes took a strong materialist stance. In contrast, the best theoretician of the Morgan group, H.J. Muller, working independently, represented the materialist extreme. Muller argued that genes must be distinct substances with extraordinary properties that allowed them to be autocatalytic (self-reproducing), to be heterocatalytic (able to make or direct the production of other kinds of molecules, especially proteins), and to retain both of these capacities after mutation. By 1922, he compared genes with what was known about bacteriophage at the time, arguing that "both possess the most remarkable property of heritable variation or 'mutability'", and looked forward to the day when "we may be able to grind genes in a mortar and cook them in a beaker" (Muller 1922). In short, he viewed genes as ultramicroscopic particles and suggested that the power of autocatalysis might be due to some structural feature of the genes or to a particular organic radical enabling them to co-opt materials from the cell to reproduce themselves.

Yet Muller recognized the extreme difficulty of pinning down the exact constitution of genes. He thought that this was primarily an *epistemological* problem—that geneticists did not yet know enough (and perhaps did not yet have good enough tools) to resolve a question that they would soon resolve. He sought to develop those tools himself and made enormously detailed experiments of various sorts to get closer to genes. For example, he and Aleksandra Prokofyeva performed exceptionally fine-grained analysis of correlations between chromosome structure and genetic effects by use of small insertions and deletions and genetic analyses of the location and fine structure of genes. They reported that small rearrangements of chromosomes were indistinguishable with available microscopic techniques from mutations of a gene: "As some of these minute rearrangements were also genetically indistinguishable from intragenic mutations, the problem of how many and what[9] supposed gene mutations are really only rearrangements assumes greater urgency" (Muller and Prokofyeva 1935).

Around the same time, a distinguished German physiological geneticist, Richard Goldschmidt, dropped his earlier support of a version of the orthodox theory and disputed the Morgan group's account of genes. Goldschmidt's research focused on how genes alter the activity or rates of formation of compounds relevant to key physiological traits (e.g., the determination of secondary sexual characters in various strains of insects, especially the gypsy moth). Although he had formerly argued that genes alter the rates of specific reactions relevant to the formation of those traits, by 1938 he came to doubt that genes are actually distinct particles or well identified submicroscopic parts of chromosomes with a separate material reality. He reasoned that there are so many things involved in bringing about genetic effects that a large region of a chromosome (perhaps even a whole chromosome) must be involved in getting any effect from a (so-called) gene. Although we can localize *mutations* rather well, he argued, they might all be constituted by *ultramicroscopic rearrangements of genetic material*, and their effects might depend on the activity of a larger region, perhaps even the whole chromosome (Goldschmidt 1938a, b). Since *detection* of genes required detection of effects of mutations or of variant alleles of the genes, and since these could not be safely distinguished from very small deletions or rearrangements, the experiments localizing *mutations* on chromosomes were correct as they stood, but *they did not justify inferences to the nature, structure, and localization of genes*. This argument magnifies the epistemological challenge regarding the difficulty of localizing genes (and determining what they are made of and how they act) into an

[9] "What" should read "which"—RMB.

ontological challenge. Goldschmidt proposed that there are no distinct entities—genes—as such. Instead, he argued, regions of chromosomes or whole chromosomes act as integrated systems, with the putative localization of individual genes (identified by the procedures to identify mutations or altered regions of chromosomes) actually serving, instead, to localize small deletions and/or rearrangements of genetic material that affected the outcome of the systematic action of the larger region or the entire chromosome.

In contemporary genetics, some of the debates about identifying genes have a similar form. Well-identified chromosomal regions have different effects in different circumstances. Exactly which products a chromosomal region (or a gene) "codes for" or produces depends on many factors, some of them in the local environment of the chromosome, some of them at large distances in the same chromosome or even on different chromosomes, some of them depending on changes in the contents of the cell during its history. What this tells us about whether we have a definite correlation between a *gene* and its products is still under debate (though the debate is not usually as radical as it was over Goldschmidt's claim that there really are no genes as such).

A second debate that began rather earlier (indeed, the roots of it preceded the rediscovery of Mendel (Burian 2005a) arose from a major controversy between two distinct biological disciplines—experimental embryology and genetics—that came to a head in the 1930s. Very roughly, the roots of the debate lay in the different questions, different organisms, and different experimental findings that were at stake in the two disciplines. Embryologists want to know, in the first instance, how an organism gets from a fertilized egg to an adult. Experimental embryology seeks to ascertain key causal steps by experiment. For its purposes, it prefers organisms with large eggs that are transparent or that can survive the removal of whatever vision-blocking membranes are in the way. Ideally, these should be organisms with many eggs that can be prepared in parallel so that the regularity of the results can be ascertained. They are even better if they tolerate experimental manipulations (transplantation of pieces, squeezing, chemical insults, etc.) Many marine organisms and some amphibians fit the bill very well. So too, do chicken eggs. Others that fit less well may still be quite useful—maize (corn in the U.S.) among plants, and some mammals that can be easily dissected at early developmental stages. But large eggs are connected with slow growth and the earliest stages of mammals are very difficult to access. In contrast, good genetic organisms have very clear pedigrees (which no marine organisms do), have short generation times (so that many generations can be checked), have strong, discretely inherited adult (or juvenile) markers that don't need to be traced back through developmental steps—a feature that allowed geneticist (by and large) to ignore the complications of development. So from ca. 1910–1940 the two disciplines generally employed different organisms, manipulated them differently, and asked different questions, with the not too surprising result that their experimental findings were discordant and that the practitioners of the disciplines built up entirely different intuitions about what to expect and how to justify those expectations.

To make these points a bit more concrete, embryologists (building on earlier results) were firmly convinced by the 1930s that a great many aspects of organismal form were determined in the cytoplasm of the egg, not the nucleus. For ease of exposition, I will speak only about animal cases. From very early on (especially in a number of marine organisms and amphibians), material from one part of the cytoplasm of the egg could be shown to be fated to contribute to some parts of the body (e.g., parts at the head end) and not others (e.g., parts at the tail end). Furthermore, constriction of an embryo could cause very specific malformations, depending on how it was done. For certain embryos, constrictions almost cutting off the head-determining end from the tail-determining end could

sometimes yield complete double embryos (identical twins); constrictions along the head-to-tail determining axis were more likely to yield a deformed embryo (Spemann 1938). Again, transplantation of material from one embryo to another, taken from the area where the early cell mass begins to invaginate (fold inward) could cause the formation of a double embryo (Spemann 1938, Spemann and Mangold 1924, translated as Spemann and Mangold 1974). This region came to be recognized to contain an organizer—a region initiating the head-to-tail organization of the embryo. Findings of this sort convinced embryologists that it wasn't the nucleus that controlled the determination of form since the cytoplasmic material was already partly determined in the egg (Burian 2005a; Gilbert 1988; Harrison 1937, 1940; Lillie 1927). So embryologists sided with Bateson[10] and others who had earlier argued in a similar way: genes cannot account for form. And if so, the geneticists' claims that genes must control all major organismal traits must be way off base. In contrast, the Morgan school and its supporters insisted that the chemical differences in the cytoplasm must already have been caused by the nucleus because the regularity of the (causal!) correlations between genetic differences and differences in adult traits were so reliable that it would only be a matter of time until they learned how genetic materials set up the cytoplasmic differences that served, somehow, to mediate between genes and the morphological traits studied by embryologists.

Since the two sides were arguing from different techniques, organisms, types of experiments, and intuitions, the disciplines of embryology and genetics stayed in strong disagreement with inadequate means to resolve their differences. From the 1920s until molecular tools began to yield new ways of addressing these matters (roughly in the 1960s), embryology and genetics simply went in different directions, largely ignoring the mutual criticisms that each had raised against the other since there was no apparent pathway to resolve their differences.

7 Interim Conclusions

These challenges to the orthodox chromosomal theory of the gene illustrate three of the principal claims that I wish to stress. First, the pursuit of different questions about genes often yield different answers about what a gene is, or is like, or how it acts. Thus, Goldschmidt's physiological genetics(in particular, his pursuit of the question of how genes act to bring about key traits) led him to challenge the chromosome theory's way of locating distinct entities (genes) as opposed to distinct mutations. Again, those who examined how genes could determine organismal form were led to challenge the power of genes as conceived by the Morgan school to accomplish the determination of form or to explain the way in which genes manage to determine the distribution and specific characteristics of different cell types within a single organism.

The investigative tools for answering each of the many questions in our set change with time and, as some groups of questions became easier to answer, the answers to one group

[10] Bateson, Morgan, and a number of the other founders of genetics, had started their career as embryologists and were strongly influenced by embryology (Gilbert 1978). But Bateson was nearly unique as a geneticist who maintained this objection to the chromosomal theory of the gene after 1915. Most of those who raised this objection were embryologists. By and large the geneticists set it aside as something requiring future research. A few physiological geneticists and a few people who migrated from embryology to genetics, such as Boris Ephrussi, kept this objection alive within genetics, and sought to develop tools to investigate how genes influence development. For some starting points on Ephrussi, see (Burian 1999; Burian et al. 1988, 1991; Sapp 1987).

of questions transform both our knowledge of genes (or the genetic material or the genetic calculus) and the plausibility of answers to the other questions. Yet the need to answer all of the questions forced the disagreements to stay on the agenda of genetics even when questions were set aside for a long time. This meant that, when pushed, geneticists generally recognized that further work to reconcile the differences that arose from focusing on different questions was still required. Goldschmidt's criticisms illustrate the point. The difficulty (given the available investigative tools) of pinning down exactly what a gene is and exactly how it acts provided an opening for a radically different view, in which *mutations* could be cleanly localized, but gene action required different, much larger boundaries for genes (or for gene action) than the Morgan school accepted on the basis of the techniques of breeding organisms plus seeking localizable mutations of known effect, carefully correlated with visible chromosomal differences.

The second point illustrated by the disputes of the 1930s is that the resolution of such conflicts often requires new technologies. Until the tools of biochemistry and/or microscopy could achieve sufficiently fine-grained analysis to allow molecular-level analyses of the genetic material or of biochemical interactions, there was no way to resolve either of the conflicts that we have just examined. The need to find new tools to explore the material of the gene, gene structure, and gene action was thoroughly recognized in the 1930s. Some tools were already being seriously explored, most particularly the use of X-rays both to cause mutations (their effectiveness in doing so was discovered in 1928 by H. J. Muller and L. J. Stadler in animals (Muller 1928) and plants (Stadler 1928). X-rays were also used in the 1930s to estimate the physical size of genes (Timofeeff-Ressovsky et al. 1935) and to gain a better understanding of the nature of mutations. We will examine the importance of technological change in the revision of gene concepts more closely in the sequel to this paper.

Conflicts like those examined here, involving divergent perspectives built up by careful experimental and theoretical work on different aspects of "the" question "what is a gene?" drove many of the changes in thinking about genes. The attempts to follow up on the different answers and to reconcile the differences between them fostered the building up of powerfully different perspectives, often starting from looks like a small, innocuous questions [for example: can you localize the differences between two variants of a gene *exactly* on a chromosome? And, if you can, where, exactly, are the boundaries of the gene?]. These perspectives drew on different investigative tools, often worked with different organisms, and always involved a different set of "core" questions (How do genes act? Where are they located? How are they organized? What are they made of?). The resolution of such conflicts often requires a change of investigative tools or a technological breakthrough that allows one or both of the conflicting groups to improve on the previous answers to their questions in a way that allows reinvestigation of their differences. The sorts of models employed in thinking about (and answering) the questions vary according to the style of work, the particular questions that are salient to an investigator or group of investigators, and the technologies they have available for attacking those questions. The need to find a new way past such impasses helps explain why, on the one hand, scientists are generally opportunists, seeking an opening that others have not exploited, and why, on the other hand, changes in the *processes* and *tools* of investigation and for adjudicating conflicting answers are often crucial to making a breakthrough that resolves some of the disagreements that have become entrenched between specific communities or groups of investigators. Recognition of the role of these sorts of changes in addressing basic questions also helps to justify my claim that overly close attention to particular models will lose

students in the trees when what they need is an overview of a larger forest, which can be provided by attention to the fundamental questions guiding research.

Conflicts like these are harder to resolve the more distant the bodies of work, that is, the more they are entrenched via the use of distinct investigative tools and traditions. Thus the disputes between embryologists and geneticists reached an impasse by 1940 and it took retooling after molecular techniques had become much more powerful before serious communication could be reestablished. Once suitable molecular tools became available to join the issues again, it became imperative to answer the question how genes could act to accomplish the sorts of developmental changes that embryologists had analyzed. This is another thread that will be picked up in the sequel to this paper.

The third point is that disputes of the sort we just examined reinforce the centrality of the tension between accounts of gene *structure* and gene *function*. That tension is pervasive and continues right up to the present day. We have already seen that early on the very definition of a gene sought to concentrate on a causal function of genes (the determination of Mendelian traits) by downplaying questions about the location, material constitution, and structure of genes. But those latter questions were key to the advances of the Morgan school. The subsequent disputes resulted from views of gene function that forced disagreements with the claims of the Morgan school; this pursuit of 'old' questions about genes was crucial to both Goldschmidt's and embryologists' denials of the effectiveness of the Morgan school's genes in bringing about the traits of organisms. As we will see in greater detail in the sequel, the question of delimiting the functions of interest turns out to play a key role in differing definitions of the gene. One hint about what is yet to come will help make the point clear: If one insists that each gene has a distinct product, then one will end up with a way of delimiting genes that differs greatly from an account of genes that allows them to make several distinct products. The current molecular understanding of how genes work has led orthodox molecular genetics to take the latter choice—a choice that was almost unthinkable for the Morgan school or in the early days of the Watson–Crick model of the gene in 1950s and 1960s! More digging is required to understand why molecular genetics has made this choice and how the choice can be covered in the process approach that I am taking here.

In this paper, I have shown that there are several guiding threads that shape the history of the science of genetics and that the elementary steps can be usefully understood by starting from the history of gene concepts and the questions that must be answered if they are to provide the basis of a coherent theory of heredity. I have also suggested that these questions help to understand the continuities of genetic research, continuities that bind together such disparate figures as Bateson, Goldschmidt, Morgan, and Muller and hinted that similar continuities shape the structure of agreements, disagreements, and of a considerable body of research in the molecular era of genetics. I have also highlighted the importance of dealing with innovations in techniques of investigation to understand how new research tools can generate findings that alter the framework established in ways that facilitate revision of previous answers to the elementary questions that underlie genetics. The burden of the sequel to this paper will be to demonstrate that this approach can facilitate students' understanding of current issues in molecular genetics.

Acknowledgments I am grateful to Kostas Kampourakis for the invitation to contribute this paper to this special issue of *Science & Education* and for his helpful comments on an earlier draft of the paper. I also appreciate the constructive criticisms of an anonymous referee and of James G. Lennox on an early draft of a related paper. These comments led to considerable improvements of the paper. All the remaining flaws are my responsibility.

Appendix: A Note on Some Resources for Educators

An especially valuable website, containing major documents bearing on the history of heredity and the development of genetics up to about 1940 is the ESP (Electronic Scholarly Publishing) project (http://www.esp.org/). The site provides useful timelines and excellent electronic reprints of numerous books and articles, including many cited in this paper, often with brief descriptions of their importance in their original context. The Mendelweb (http://www.mendelweb.org/) provides several useful versions of Mendel's key paper plus a variety of useful commentaries. The best single technical history of genetics to 1940 is (Carlson 1966, but see also his more general text, Carlson 2004).

References

Adams, M. B. (Ed.). (1990). *The wellborn science: Eugenics in Germany, France, Brazil, and Russia*. New York and Oxford: Oxford University Press.

Allen, G. E. (1978). *Thomas Hunt Morgan: The man and his science*. Princeton, NJ: Princeton University Press.

Allen, G. E. (1979). Naturalists and experimentalists: The genotype and the phenotype. *Studies in the History of Biology, 3*, 179–209.

Bachelard, G. (1934/1999). *Le nouvel esprit scientifique*. Paris: Presses Universitaires de France (first ed. 1934, 7th ed. 1999).

Bateson, W. (1913). *Problems of genetics*. New Haven, CT: Yale University Press.

Beurton, P. J., Falk, R., & Rheinberger, H.-J. (Eds.). (2000). *The concept of the gene in development and evolution: Historical and epistemological perspectives*. Cambridge and New York: Cambridge University Press.

Boveri, T. (1902). Über mehrpolige Mitosen als Mittel zur Analyse des Zellkerns. *Verhandlungen der physikalischen-medizinischen Gesellschaft zu Würzburg, 35*, 67–90.

Boveri, T. (1968). On multipolar mitoses as a means for the analysis of the cell nucleus. In B. R. Voeller (Ed.), *The chromosome theory of inheritance* (pp. 85–94). New York: Appleton-Century-Crofts.

Burian, R. M. (1981–1982). Human sociobiology and genetic determinism. *Philosophical Forum, 13*, 40–66.

Burian, R. M. (1982). [Review of] Bateson, W., *Problems of genetics*. *Philosophy of Science, 49*, 147–149.

Burian, R. M. (1987). Realist methodology in contemporary genetics. In N. Nersessian (Ed.), *The process of science* (pp. 195–210). Dordrecht: Nijhoff.

Burian, R. M. (1993a). How the choice of experimental organism matters: Reflections on an epistemological aspect of biological practice. *Journal of the History of Biology, 26*, 351–367.

Burian, R. M. (1993b). Unification and coherence as methodological objectives in the biological sciences. *Biology and Philosophy, 8*, 301–318.

Burian, R. M. (1997). Exploratory experimentation and the role of histochemical techniques in the work of Jean Brachet, 1938–1952. *History and Philosophy of the Life Sciences, 19*, 27–45.

Burian, R. M. (1999). Boris Ephrussi on the units of inheritance and of development. In C. Galperin, S. F. Gilbert, & B. Hoppe (Eds.), *Fundamental changes in cellular biology in the 20th century: Biology of development, chemistry and physics in the life sciences* (pp. 121–131). Tournhout, Belgium: Brepols.

Burian, R. M. (2000). On the internal dynamics of Mendelian genetics. *Comptes rendus de l'Académie des Sciences, Paris. Série III, Sciences de la Vie/Life Sciences, 323*, 1127–1137.

Burian, R. M. (2004). Molecular epigenesis, molecular pleiotropy, and molecular gene definitions. *History and Philosophy of the Life Sciences, 26*, 61–81.

Burian, R. M. (2005a). Lillie's paradox—or, some hazards of cellular geography. *The epistemology of development, genetics, and evolution* (Chap. 10, pp. 183–209). New York: Cambridge University Press.

Burian, R. M. (2005b). Reconceiving animals and their evolution: On some consequences of new research on the modularity of development and evolution. *The epistemology of development, genetics, and evolution* (Chap. 12, pp. 234–261). New York: Cambridge University Press.

Burian, R. M. (2007). On microRNA and the need for exploratory experimentation in post-genomic molecular biology. *History and Philosophy of the Life Sciences, 29*, 285–312.

Burian, R. M., Gayon, J., & Zallen, D. (1988). The singular fate of genetics in the history of French biology, 1900–1940. *Journal of the History of Biology, 21*, 357–402.
Burian, R. M., Gayon, J., & Zallen, D. (1991). Boris Ephrussi and the synthesis of genetics and embryology. In S. Gilbert (Ed.), *A conceptual history of embryology* (pp. 207–227). New York: Plenum.
Burian, R. M., & Zallen, D. T. (2009). Genes. In P. J. Bowler & J. V. Pickstone (Eds.), *Cambridge history of the life and earth sciences* (pp. 432–450). Cambridge: Cambridge University Press.
Carlson, E. A. (1966). *The gene: A critical history*. Philadelphia and London: W. B. Saunders.
Carlson, E. A. (1974). The drosophila group: The transition from the Mendelian unit to the individual gene. *Journal of the History of Biology, 7*, 31–48.
Carlson, E. A. (1989). *The gene: A critical history*. Ames, IA: Iowa State University Press.
Carlson, E. A. (2004). *Mendel's legacy: The origin of classical genetics*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.
Corcos, A., & Monaghan, F. V. (1992). *Gregor Mendel's experiments on plant hybrids. A guided study*. New Brunswick, NJ: Rutgers University Press.
Cuénot, L. (1903). L'hérédité de la pigmentation chez les souris (2me note). *Archives de Zoologie Expérimentale et Générale* 4e sér., 1: 33–41.
Darden, L. (1991). *Theory change in science: Strategies from Mendelian genetics*. New York: Oxford University Press.
De Vries, H. (1889). *Intracellulare pangenesis*. Jena: Gustav Fischer.
De Vries, H. (1901). *Die Mutationstheorie*. Leipzig: Veit & Co.
De Vries, H. (1909–1910). *The mutation theory: Experiments and observations on the origin of species in the vegetable kingdom*. London and Chicago.
De Vries, H. (1910). *Intracellular pangenesis*. Chicago: Open Court.
Galton, F. (1865). Hereditary talent and character. *Macmillan's Magazine*, 12(68), *12*(71), 157–166, 318–327.
Galton, F. (1869). *Hereditary genius*. London: MacMillan.
Galton, F. (1871a). Experiments in pangenesis, by breeding from rabbits of a pure variety, into whose circulation blood taken from other varieties had previously been transfused. *Proceedings of the Royal Society, London, 19*, 393–410.
Galton, F. (1871b). Pangenesis. *Nature, 4*, 5–6.
Galton, F. (1883). *Enquiries into human faculty*. London: Macmillan.
Gayon, J., & Burian, R. M. (1999). The French school of genetics: From physiological and population genetics to regulatory molecular genetics. *Annual Review of Genetics, 33*, 313–349.
Gericke, N. M., & Hagberg, M. (2007). Definition of historical models of gene function and their relation to students' understanding of genetics. *Science & Education, 16*, 849–881.
Gilbert, S. F. (1978). The embryological origins of the gene theory. *Journal of the History of Biology, 11*, 307–351.
Gilbert, S. F. (1988). Cellular politics: Goldschmidt, Just, Waddington and the attempt to reconcile embryology and genetics. In R. Rainger, K. R. Benson, & J. Maienschein (Eds.), *The American development of biology* (pp. 311–346). Philadelphia: University of Pennsylvania Press.
Goldschmidt, R. B. (1938a). *Physiological genetics*. New York: McGraw-Hill.
Goldschmidt, R. B. (1938b). The theory of the gene. *Scientific Monthly, 46*, 268–273.
Harrison, R. G. (1937). Embryology and its relations. *Science, 85*, 369–374.
Harrison, R. G. (1940). Cellular differentiation and internal environment. In F. G. Moulton (Ed.), *The cell and protoplasm* (pp. 77–97). Washington: The Science Press.
Johannsen, W. (1909). *Elemente der exakten Erblichkeitslehre*. Jena: G. Fischer.
Kampourakis, K. (2012). Mendel and the path to genetics: Portraying science as a social process. *Science and Education* 21: In Press; preprint available from the Journal's website.
Kohler, R. E. (1994). *Lords of the fly: Drosophila genetics and the experimental life*. Chicago: Chicago University Press.
Kühl, S. (1994). *The Nazi connection: Eugenics, American racism, and German National socialism*. New York and Oxford: Oxford University Press.
Lillie, F. R. (1927). The gene and the ontogenetic process. *Science, 64*, 361–368.
Maienschein, J. (1991). *Transforming traditions in American biology, 1880–1915*. Baltimore and London: Johns Hopkins University Press.
Mendel, G. (1865). Versuche üvwe Pflanzenhybriden. *Verhandlungen des naturforschenden Vereines, Abhandlungen, Brünn* IV. 3–47. Also available at *Mendel Web* http://www.mendelweb.org/MWGerText.html and at http://www.esp.org/foundations/genetics/classical/gm-65-f.pdf.
Mendel, G. (1869). Über einige aus künstlichen Befruchtung gewonnen Hieracium-Bastarde. *Verhandlungen des naturforschenden Vereines, Abhandlungen, Brünn*, *VIII*, 26–31.

Mendel, G. (1909). On Hieracium-hybrids obtained by artificial fertilisation. In W. Bateson (Ed.), *Mendel's principles of heredity*. Cambridge: Cambridge University Press. Appendix; pp. 362–369. Also available in Stern and Sherwood (1966) and at the Mendel Web http://www.mendelweb.org/Mendel.html and at http://www.esp.org/foundations/genetics/classical.

Mendel, G. (1966). Experiments on plant hybrids. In C. Stern & E. Sherwood (Eds.), *The origin of genetics: A Mendel sourcebook* (pp. 1–48). San Francisco: W. H. Freeman and Co. Also available at *Mendel Web* http://www.mendelweb.org/Mendel.html and at http://www.esp.org/foundations/genetics/classical/.

Morgan, T. H. (1910a). Chromosomes and heredity. *American Naturalist, 44*, 449–496.

Morgan, T. H. (1910b). Sex limited inheritance in drosophila. *Science, 32*, 120–122.

Morgan, T. H. (1911a). An attempt to analyze the constitution of the chromosomes on the basis of sex-limited inheritance in Drosophila. *Journal of Experimental Biology, 11*, 365–412.

Morgan, T. H. (1911b). The origin of five mutations in eye color in Drosophila and their modes of inheritance. *Science, 33*, 534–537.

Morgan, T. H. (1911c). The origin of nine wing mutations in Drosophila. *Science, 33*, 496–499.

Morgan, T. H. (1911d). Random segregation versus coupling in Mendelian inheritance. *Science, 34*, 384.

Morgan, T. H., Sturtevant, A. H., Muller, H. J., & Bridges, C. B. (1915). *The mechanism of Mendelian heredity*. New York: Henry Holt and Co.

Muller, H. J. (1922). Variation due to change in the individual gene. *American Naturalist, 56*, 32–50.

Muller, H. J. (1928). The measurement of gene mutation rates in drosophila, its high variability, and its dependence upon temperature. *Genetics, 13*, 279–357.

Muller, H. J. (1946). Thomas Hunt Morgan, 1866–1945. *Science, 103*, 550–551.

Muller, H. J., & Prokofyeva, A. A. (1935). The individual gene in relation to the chromomere and the chromosome. *Proceedings of the National Academy of Sciences, USA, 21*, 16–26.

Müller-Wille, S., & Orel, V. (2007). From Linnaean species to Mendelian factors: Elements of hybridism, 1751–1870. *Annals of Science, 64*, 171–215.

Newman, S. A. (2007). William Bateson's physicalist ideas. In J. Maienschein & M. D. Laubichler (Eds.), *From embryology to evo-devo* (pp. 83–107). Cambridge, MA: MIT Press.

Olby, R. C. (1979). Mendel no Mendelian? *History of Science, 17*, 53–72.

Olby, R. C. (1985). *Origins of Mendelism*. Chicago: University of Chicago Press.

O'Malley, M. A., Elliott, K. C., & Burian, R. M. (2010). From genetic to genomic regulation: Iterativity in microRNA research. *Studies in history and philosophy of biological and biomedical sciences, 41,* 407–417.

Provine, W. B. (1971). *The origins of theoretical population genetics*. Chicago: Chicago University Press.

Sapp, J. (1987). *Beyond the gene: Cytoplasmic inheritance and the struggle for authority in genetics*. New York: Oxford University Press.

Smith, M. U., & Adkison, L. R. (2010). Updating the model definition of the gene in the modern genomic era with implications for instruction. *Science & Education, 19*, 1–20.

Special Issue. (2000). The rediscovery of Mendel's laws. *Comptes rendus de l'Académie des Sciences, Paris. Série III, Sciences de la Vie/Life Sciences, 323*(12), 1035–1174.

Spemann, H. (1938). *Embryonic development and induction*. New Haven: Yale University Press.

Spemann, H., & Mangold, H. (1924). Über Induktion von Embryonalanlagen durch Implantation artfremder Organisatoren. *Wilhelm Roux' Archiv für Entwicklungsmechik der Organismen, 100*, 599–638.

Spemann, H., & Mangold, H. (1974). Induction of embryonidc primordia by implantation of organizers from a different species. In B. H. Willier & J. M. Oppenheimer (Eds.), *Foundations of experimental embryology*. New York: Hafner.

Stadler, L. J. (1928). Genetic effects of X-Rays in maize. *Proceedings of the National Academy of Sciences, USA, 14*, 69–75.

Stadler, L. J. (1954). The gene. *Science, 120*, 811–819.

Stern, C., & Sherwood, E. R. (Eds.). (1966). *The origin of genetics, a Mendel source book*. San Francisco: W. H. Freeman and Co.

Sturtevant, A. H. (1913). The linear arrangement of six sex-linked factors in drosophila, as shown by their mode of association. *Journal of Experimental Zoology, 14*, 43–59.

Sturtevant, A. H. (1959). Thomas Hunt Morgan. *National Academy of Sciences, USA. Biographical Memoirs, 33*, 283–325.

Sutton, W. S. (1902). On the morphology of the chromosome group in *Brachystola magna*. *Biological Bulletin, 4*, 24–39.

Sutton, W. S. (1903). The chromosomes in heredity. *Biological Bulletin, 43*, 231–251.

Thieffry, D., & Burian, R. M. (1996). Jean Brachet's scheme for protein synthesis. *Trends in Biochemical Sciences, 26*, 114–117.

Timofeeff-Ressovsky, N. W., Zimmer, K. G., & Delbrück, M. (1935). Über die Natur der Genmutation und der Genstrucktur. *Nachrichten der Gesellschaft für Wissenschaften, Göttingen 6 NF, Nr, 13*, 190–245.