

On the internal dynamics of mendelian genetics

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Abstract – This paper offers a revisionist account of the development of Mendelian genetics, focusing on the ‘problem of the gene’, 1900–1930. I examine conflicting claims about the composition, location, and action of genes posed by Bateson, the Morgan group, and Goldschmidt. Their research programs focused on different phenotypes and were based on different assumptions about the nature of genes. The problem of the gene transcended such specific research programs, but their findings had to be taken into account to solve it. The need to resolve conflicting claims drove Mendelian geneticists to exploit the resources and invade the turf of other disciplines in their search for a sound characterization of the gene. The problem of reconciling conflicting views greatly influenced the development of genetics and provided the stimulus for many of the discoveries made by geneticists from 1900 to 1940. © 2000 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

Mendelian genetics / history of genetics

Résumé – **Sur la dynamique interne du mendélisme.** Cette communication, centrée sur « le problème du gène » présente une interprétation révisée du développement de la génétique mendélienne dans la période 1900–1930. L’on y examine les assertions conflictuelles de Bateson, du groupe de Morgan, et de Goldschmidt sur la composition, la localisation, et l’action des gènes. Les programmes de recherche de ces biologistes renvoyaient à des phénotypes différents, et étaient fondés sur des postulats différents quant à la nature des gènes. Le problème du gène transcendait ces programmes de recherche spécifiques, mais leurs découvertes devaient être prises en compte pour résoudre ce problème. La nécessité de dépasser la divergence des postulats a conduit les Mendéliens à exploiter les ressources d’autres disciplines pour caractériser le gène. Les problèmes soulevés par la réconciliation de perspectives conflictuelles a considérablement influencé le développement de la génétique et a stimulé de nombreuses découvertes en génétique de 1900 à 1940. © 2000 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS

génétique mendélienne / histoire de la génétique

“To become a science, [for much of the 19th century] biology had to cut itself off radically from physics and chemistry. To continue investigation of the structure and functioning of living beings in the middle of the 20th

century, biology had to cooperate closely with them. From this union, molecular biology was born.” ([1], pp. 245–246)

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1. Introduction

I present a revisionist picture of the development of Mendelian genetics in this paper, with the ‘problem of the gene’ as a guiding thread. I focus on the large-scale internal dynamics that drove Mendelian genetics and argue that Mendelians were forced into a dialectic relationship with each other and with other disciplines in pursuing the problem of the gene. The main point of the paper is to gain better understanding of the dynamics of the development of genetics itself. The key issue is to understand the relationship between the general constraints geneticists placed on satisfactory accounts of the gene and the various programs of detailed mechanistic work they employed to gain access to the genetic material and gene action. Along the way, I will address some points about the social character of the discovery process.

One central concern is the tension between the view that genes are formal entities, i.e. calculational devices, and the view that genes have material reality. Once the material reality of genes is taken seriously, it raises many important questions. The following groups cover the more obvious questions.

- Where are genes located? How many genes are there?
- How are they duplicated and transmitted across generations?
- What are genes made of? How are they internally organized, structured and individuated?
- What about their physiology? What metabolic processes and regulatory interactions do they enter into? How does cellular physiology affect their construction, structure, and behavior?
- How do genes affect, specify, or alter the characters of the organism? Do they control the sequence in which traits arise in the development of the organism? If so, how? If not, what does?
- How are they changed in mutation so that they can yield altered versions of the traits they affect and still be duplicated?

The resources available for answering these questions around 1900, especially the experimental technologies, were very limited. Yet, given the experimental turn at the end of the 19th century each of these questions called for experimental investigation, using more-or-less mechanist-reductionist tactics. Each question was more limited than the entire group of questions, but the available experimental tools were not adequate to resolve any of them. Accordingly, particular questions were addressed opportunistically, employing tools developed in other disciplines as they became available. Some questions were addressed by working with restricted groups of organisms, but it was often impossible to determine which results were peculiar to those organisms and which had general validity – witness the difficulties arising from the differences in the behavior of *Pisum* and *Hieracium*, *Oenothera* and *Drosophila*, or the relative simplicity of the chromosomal cytology of *Ascaris* as compared with sea urchins. Agriculturalists, who typically worked with a few economically

important organisms, came to use the Mendelian apparatus to answer particular questions about their organisms, but often did not seek to base theoretical accounts of genes on their findings. This configuration of circumstances and tools made progress in dealing with basic questions, which occurred in sudden, concentrated bursts, very uneven. When specialized investigations or programs of research generated results bearing on basic questions, the answers had to be fed back to the entire group of questions bearing on the problem of the gene, a process that required geneticists to stand back and adopt a synthetic point of view.

This last task was complicated by the unevenness of the progress in handling different groups of questions. Work on the different groups yielded conflicting intuitions and proposals about the nature of the gene. For at least a half century there was no fully satisfactory concrete answer to any of the basic questions on our list except for questions about where genes are located and how they are transmitted across generations (and even here the answers were often challenged). For this reason, genes were normally treated as black boxes, identified primarily by their effects and by the patterns in which those effects were transmitted across generations. This invisibility of genes was crucial; it meant that one had to employ theoretical considerations in approaching the problem of the gene and to do a great deal of work to link theory with experiment. Furthermore, with the exception of breeding experiments, experimental approaches to the various questions were not supplied directly by genetic theory. In consequence, geneticists were often forced to work opportunistically, as amateurs, in other domains in order to appropriate new experimental technologies and to link their theoretical and experimental work to work in other biological theories and disciplines. This aspect of my picture is crucial for understanding the dynamics of discovery in genetics.

Before turning to the beginning of the century, it is worth insisting on the power of the problem of the gene. Well into the 1950s, key geneticists treated the gene, paradoxically, both as a material thing with defined effects and a concrete, but imprecisely known, location and as an abstraction, a formal entity that could be redefined to suit the theoretical context [2–4]. Thus, in a valedictory article, “The Gene” ([5], see also [4], p. 139), L.J. Stadler, who considered the correlations between breeding data and cytological results as part of the operationally observable phenomena, distinguished two conceptions of the gene. These are the ‘operational gene’, defined as “the smallest segment of the gene-string that can be shown to be consistently associated with the occurrence of a specific genic effect”, and the theoretically defined ‘hypothetical gene’, a presumptive material entity, individuated as a material object over and above its association with a part of a chromosome, but otherwise defined by whatever theory was being tried out. Stadler argued that there were no adequate criteria for choosing between alternative ways of picking out hypothetical genes. Thus, “[The operational gene] cannot be defined as a single molecule, because we have no experimental operations that can be applied in

actual cases to determine whether or not a given gene is a single molecule. It cannot be defined as a single unit, because, although our definition provides that we will recognize as separate genes any determiners actually separated by crossing over or translocation, there is no experimental operation that can prove further separation is not possible. For similar reasons it cannot be defined as the unit of reproduction or the unit of action of the gene-string, nor can it be shown to be delimited from neighboring genes by definite boundaries" ([5], p. 814).

In consequence, Stadler thought that most work should be based on the operational gene. He complained that "the term *gene* as used in current genetic literature means sometimes the operational gene, and sometimes the hypothetical gene, and sometimes, it must be confessed, a curious conglomeration of the two" [5]. This made attempts to define or individuate genes tantalizing and frustrating. No theory of the gene was adequately supported and, as operationally defined, the physical embodiment, chemical constitution, and precise location of genes remained unknown. By the time they acquired material reality in the form of specific stretches of DNA (and, occasionally, RNA), their boundaries were not as precise as classical Mendelian genetics had anticipated. Indeed, even now we have no uniquely satisfactory way to divide the genetic material up into genes [2, 6–8]. But that is a matter for another paper.

2. Early attempts to define and delimit genes

Recently there has been considerable controversy about the interpretation of Mendel's "Versuche über Pflanzen-Hybriden" [9] and its reinterpretation by the founders of genetics (see, e.g., [10–15]). In his paper Mendel used the words 'Factor(en)' twice and 'Elemente(n)' ten times, but clearly did not mean 'genes' by them. I illustrate his usage by quoting the one relevant use of the word 'Factoren'. Sherwood, whose translation is faithful to the German original, renders the passage thus:

"[F]urther experiments... appear fitted to afford some conclusions as regards the composition of the egg and pollen cells of hybrids... An important clue is afforded in *Pisum* by the circumstance that among the progeny of the hybrids constant forms appear, and that this occurs, too, in respect of all combinations of the associated characters. So far as experience goes, we find it in every case confirmed that constant progeny can only be formed when the egg cells and the fertilizing pollen are of like character, so that both are provided with the material for creating quite similar individuals, as is the case with the normal fertilization of pure species. We must therefore regard it as certain that exactly similar factors must be at work also in the production of the constant forms in the hybrid plants. Since the various constant forms are produced in one plant, or even in one flower of a plant, the conclusion appears logical that in the ovaries of the hybrids there are

formed as many sorts of egg cells, and in the anthers as many sorts of pollen cells, as there are possible constant combination forms, and that these egg and pollen cells agree in their internal compositions with those of the separate forms" ([16], p. 24).

Here, Mendel uses the evidence for what were later interpreted as segregation and purity of the gametes to show that there are at least as many types of germ cells as there are combinations of traits that become constant in the progeny derived from a hybrid. A self-fertilizing plant is a hybrid if it has a trait that does not breed true, but allows the extraction of constant forms of the trait in its progeny. The constancy of the traits in subsequent generations provides the sole evidence that two germ cells shared the same "internal compositions". This is the one thing that Mendel has to be committed to when he claims that "exactly similar factors must be at work" in the germ cells of the plants – and he provides no clues about the intrinsic nature of these 'factors'. Mendel's uses of 'Elementen' (all in the Concluding Remarks) and 'Factoren' are entirely concordant. The text allows no secure conclusions about the number, nature, or locations of the factors in the gametes. All we know is that they account for the constancy of forms and that, when crossed into a hybrid, they reside jointly in the plant, but are separated again in the germ cells. This is how self-fertilization can yield both constant and inconstant offspring.

The 'rediscovery' of Mendel occurred after many important biologists had turned against evolutionary speculation, among other reasons because of the unresolvable debates about the reconstruction of phylogenies initiated by Haeckel. Darwinism was especially unpopular at the turn of the century because of increasing doubts about the adequacy of natural selection to account for the origin of species [17, 18]. At the time agriculturalists were also increasingly interested in understanding hybrids and crosses and many biologists sought to focus on topics that could be definitively resolved by means of concrete experiments. They argued that the turn to experiment was necessary to make biology 'more scientific'. It was no accident that all three 'rediscoverers' were already doing hybridization experiments on plants and keenly aware of developments in cytology. But it is also no accident that by 1905 De Vries, who applied his work on heredity to more speculative evolutionary and developmental questions, did not remain in the Mendelian mainstream.

By 1910, Mendelism was deeply committed to basing its claims on experiment. Thus, to deal with evolution it was required to demonstrate experimentally the workings of a mechanism that could yield speciation. But it was risky to make large claims about the importance of such mechanisms in evolution for fear of reigniting sterile debates with those who thought other mechanisms to be more important. Such speculations, whether they concerned the course of evolution or the material of which genes were made, were experimentally unresolvable and practically unimportant. There are interesting connections here to Harwood's treatment of 'mandarin' and 'prag-

matic' styles in genetics [19]. Very roughly, the mandarin style is synthetic, wishing to take account of all relevant branches of learning to reach an integrated descriptive–explanatory theory. Although the mandarin style remained dominant in Germany, internationally it lost ground during the decade 1910–1920, especially after World War I. In this decade the mainstream of research in genetics came to be dominated by Americans, who were preponderantly pragmatic in style. Of particular importance here was the central role of practically oriented agricultural work, which contributed to the expansion of genetics in the US [20] and the success of the Morgan group. In any event, the 'pragmatic' style came to dominate mainstream Mendelian genetics in spite of the efforts of Correns, Delage [21], Goldschmidt, Johannsen, De Vries [22], and many others to keep the connection between genetics and the larger issues of *allgemeine Biologie* (general biology).

Three important transitional figures who combined aspects of both styles, W. Bateson, W. Johannsen, and H. De Vries, deserve some attention in this connection. All three retained the aspiration to deal with grand problems. All three were able experimenters who employed breeding experiments in practical contexts and applied them to the problem of the gene. All three were saltationists and, to that extent, anti-Darwinians. But Bateson and Johannsen's later saltationism was more limited than that of De Vries; because of their epistemological conservatism they were more reluctant to claim that their findings provided decisive support for saltationism. Johannsen's famous experiments on pure lines of *Phaseolus* showed that the average weight of the seeds in these highly homozygous beans was subject to 'fluctuating variation'. Johannsen ascribed the variation to microenvironmental differences and demonstrated that fluctuating variations are not inherited within a few generations. He argued that these results show that the homozygotes do not change their hereditary constitution except by mutation. Thus, pure lines contain no variation on which natural selection could operate to transform the features of the line [23, 24]. Believing that pure lines were a good model for the composition of the fundamental units in natural populations, he argued (reasonably, but mistakenly) that his findings supported De Vries's mutationism by showing that there is not enough genetic variation in natural populations to allow selection to transform them into new species.

Johannsen was firmly convinced of the correctness of this stand. However, he also distinguished between speculative evolutionary biology (*Deszendenzlehre*) and the study of inheritance (*Erblichkeitsforschung*) [24]. He remained reserved about the extrapolation to evolution, which went far beyond the experimental support for mutation as the primary source of variation and the available experimental knowledge of the composition of natural populations. (For alternative views on Johannsen, see, e.g., [25–27].) Many pragmatically oriented geneticists utilized this restriction of the proper domain of genetics to argue against connecting genetics to such evolutionary speculations.

Johannsen remained even more cautious in extrapolating from his experimental findings to the nature of genes. Indeed, he explicitly introduced the new term 'gene' as a replacement for De Vries's more committal 'pangen' (connected to the tradition of treating hereditary particles as *Anlagen* that somehow specified or represented a particular organ or character) in order to provide a word free of evolutionary and theoretical speculation:

"[The term 'gene'] should express only the simple conception that the characteristics of an organism are, or can be, caused or co-determined by 'something' in the make-up [*Konstitution*] of the gametes. The word 'gene' is thus completely free of any hypothesis. It expresses only the fact that the characteristics of the organism are determined in the make-up of the gametes by particular 'conditions', 'factors', 'units', or 'elements'. These are at least partially separable and thus to some extent independent—in short, exactly what we wish to call genes" ([24], pp. 143–144, my translation). (Compare Carlson's translation from the first edition of 1909 ([4], pp. 20–21).)

This passage already reveals the tension between 'operational' and 'hypothetical' genes. Operational genes (for Johannsen strictly correlations of breeding data, not including chromosomal locations) could be Pearsonian or Machian constructs. That is, they could be formal constructs comparable to average family size – logical constructions that represent breeding data or (later) a combination of breeding and chromosomal data. On such an account, genes need not have separate material existence, but are the most suitable formal means for representing Mendelian ratios and the improvements on those ratios achieved by models of coupling and repulsion, reduplication, linkage, and the like. This sort of formal genetics was the target of various criticisms. Thus, before T.H. Morgan converted to Mendelism, he held that Mendelian doctrine was empty because it allowed one to analyze any outcome of breeding experiments in terms of genes if one simply employed enough interacting genes ([28], p. 365).

The Machian approach influenced formal genetics, especially quantitative genetics, which was developed particularly for 'continuous' traits of agricultural interest such as milk production, oil content, body or fruit weight, etc. Its equations started from phenotypic variables and calculated the number of genes involved in altering such traits post facto from breeding data on phenotypic change. The point of determining the number of genes was to develop a practical breeding program to improve the phenotype of crops, farm animals, and fancy breeds. For economic breeding, what matters is the ability to improve the yield or other desired property of a breed (often based on the 'breeding value' of the individual), not getting a correct account of the physical constitution of the germ cells or a uniquely correct count of the number of genes.

Turning to the alternative interpretation, according to which genes are material entities, conditions, or states, in interpreting the views of the pioneers it is important not to slip too quickly into thinking of the entities in question as molecules. Many proponents of the reality of genes held

significantly different views. Thus Bateson argued firmly against the view that genes could be material particles. He held privately that genes are probably something like stable harmonic resonances. If correct, this would enable one to understand how genes could guide development and shape the form of an organism. Furthermore, harmonic resonances would allow one to model the addition of new units to a meristic series by increasing the number of nodes of a standing wave. Such changes would be saltational – note that as one increases the length of a string or a resonance chamber, a standing wave shifts abruptly from having n nodes to $n + 1$ and that there are no standing waves with $n + 1/2$ nodes. Since there are no organisms with partial vertebrae or segments, not even in teratology, Bateson thought that this result fit nicely with his views about discrete variation in nature. Chapters II and III of his *Problems of Genetics* (1913) deal with meristic phenomena and segmentation, thus indicating the importance he attached to these topics. Arguing against the possibility that genes could be material particles, he wrote:

“When we pass from the substantive to the meristic characters, the conception that the character depends on the possession by the germ of a particle of a specific material becomes even less plausible. Hardly by any effort of imagination can we see any way by which the division of the vertebral column into x segments or into y segments, or of a Medusa into 4 segments or into 6, can be determined by the possession or by the want of a material particle... If we are to look for a physical analogy at all we should rather be led to suppose that these differences in segmental members corresponded with changes in the amplitude or number of dividing waves than with any change in the substance or material divided” ([29], p. 35).

However, he was unable to produce mathematical or experimental evidence for these speculations, so he did not publish any more on them [3, 4, 30, 31].

Another reason for caution in interpreting genes in terms of molecules during the first 30 years of the last century is the great influence of the colloidal theory of the chemical constitution of the cell. That theory made the molecular weight and composition of chemically active agents in the cell indeterminate [32, 33]. The difficulties that Hermann Staudinger faced in setting forth an acceptable account of macromolecules in the 1920s and 1930s, described by Olby [32], illustrate the point. The available chemistry simply was not adequate for the purposes of geneticists who wished to provide an account of the molecular structure of genes.

It is hard to determine precisely where such epistemologically conservative figures as Bateson and Johannsen come down on these interpretive issues. Both opposed the chromosome theory and sought to define genes atheoretically, independent of their speculations about the constitution of genes. Yet they and many of their successors were implicitly committed to the reality of genes, interpreted as unknown entities whose composition and structure we might someday characterize correctly. They both denied that definitional restrictions could pin down the nature of

that reality. As we shall see, they also put constraints on the solution of the problem of the gene that Morgan and his colleagues did not and interpreted the additional restrictions as militating against the chromosomal theory.

3. How were genes identified?

The example of quantitative genetics illustrates a key point. One's conception of the phenotype greatly affects the conception of the genotype. The choice of traits to examine significantly affects what can count as genes and how to enumerate them. Consider this point first from the side of the gene. Though it is not what Johannsen intended, the usual interpretations of his concept of the gene treat it as a 'referentially open functional concept'. This philosophical term indicates the semantic status of the term 'gene'. The term is not associated with an intrinsic characterization of genes. Rather, alleles are identified and individuated by specifying some effect for which they are responsible and by specifying constraints that localize or particularize the causal agent, ideally well enough to pick out a single entity from among those responsible for the effect. 'Referential openness' indicates that the sort of thing (molecule? part of a chromosome? harmonic resonance?) referred to by the term 'gene' is indeterminate. Classical genetics could not determinately characterize the material, structure, or mode of action of genes.

Furthermore, classical genetics offered no direct way to recognize the presence, as such, of a gene. To detect genes there had to be at least two alleles yielding detectably distinct effects. In short, to identify genes, the trick was to find observable differences between two phenotypes that were transmitted in Mendelian style. The method for determining that the differences were due to variants of a gene was simply a more sophisticated version of Mendel's test in terms of the 'constant' and 'inconstant' forms produced by hybrids. The greater sophistication took account of more subtle trait differences than Mendel employed, more complicated modes of transmission (e.g. sex linkage), and special circumstances (recessive lethals, variable penetrance, polygeny, gene interactions (including non-additive interactions), cytoplasmic effects, nutritional influences, etc.). Nonetheless, the basic scheme was fairly simple in principle. Typically, one allele was considered to be the 'wild type' and the others to result from mutation of the 'wild type'. Since most 'wild type' alleles had undergone a long history of natural selection, they were generally assumed to have been honed by a process of adaptation. Accordingly, the function of the 'wild type' allele was usually thought to be to produce the effect disrupted by the mutation for which the gene was named.

Consider, for example, the *Drosophila* gene *vermillion* (hereafter *v*) discovered by the Morgan group before 1916 ([34], p. 27) in work begun with a fly whose eye color was vermillion rather than red, the wild type. Breeding experiments demonstrated sex-linked inheritance of the color and the factor in question was quickly associated with a region of the X chromosome. Later investigations estab-

lished that *v* flies lack a brown pigment, one of two main pigments that produce the red eye color. The name of the allele reflects the salient feature of mutant flies. This was the usual convention; the names of genes did not describe the function of the wild type, but the departure from it produced by an unusual allele. (Thus, *v*⁺ came to designate the wild type. The superscript can be interpreted as 'the wild type corresponding to __'.) In this case, somewhat unusually, it was possible to specify more closely a particular effect of possessing the wild type allele. The specific function of *v*⁺ was required for the production of the brown pigment. In short, the wild type allele of *v* is associated with the *v* region of the X chromosome and is required for normal production of the brown pigment.

In 1924 *v* was distinguished from an allele of another gene. This allele, *cinnabar* (*cn*) was associated with a region of the second chromosome; homozygous *cn* has nearly the identical effect on eye color as *v* [35]. The wild type allele of *cn* is also required for formation of the brown pigment. Two different sorts of findings showed that *cn* is distinct from *v*. First, breeding experiments associated *cn* with a different chromosome than *v*; thus, the two genes are inherited independently of one another. Second, in the mid 1930s, Beadle and Ephrussi showed, via a fascinating detour involving implantation of imaginal disks, that *v* affects an earlier step in the chain of events leading to production of the brown pigment than *cn*. Thus, follow-up work showed that the two genes have different functions. (This story, too complicated to recount here, is well covered in [36].)

An unavoidable difficulty with referentially open functional concepts is that distinct entities with distinct effects may be mistaken for each other unless the function is spelled out precisely. The *v*–*cn* case suffices to make the initial point. To distinguish *v* from *cn* it is not enough to describe the function of their wild type alleles as production of the brown pigment. Both wild type genes are required for normal production of this pigment. While the difference in chromosomal location enables one to distinguish the two genes, it is only when one specifies the steps in the synthetic chain that are affected that it is clear that the genes differ in function, and hence probably in structure as well. This feature of referentially open function concepts points to the close connection between the way in which we characterize the function of a gene and what can count as an adequate intrinsic characterization of that gene. (For further development of these points, see various essays in [2].)

4. How does choice of phenotype influence the definition of the gene?

For the first half of the last century, anyone who thought genes to be more than a *façon de parler* had to identify them by using a referentially open functional concept of the gene. This is far more important than it might seem at first glance. The identification of genes by phenotypic

differences associated with alternative alleles is covertly sensitive to the range and types of phenotypes taken into account. By focusing on this procedure from the side of the phenotype we will discover deep connections to our list of obvious questions about genes and uncover reasons for geneticists to work closely with biologists from other disciplines.

Consider Bateson's views, already discussed. His interest in development and in meristic variation focused his attention on such topics as how differences in genes could yield differences in the numbers in a meristic series. Since he held that material particles are fundamentally inert, he was convinced that, in principle, this problem could not be solved with particulate genes. In contrast, even without a satisfactory account of the details, at least standing waves and stable harmonic resonances could do so in principle. Thus, sometime before 1913, he held that an adequate definition of genes must require them to be the sorts of things that can account for meristic differences in the morphology of different organisms. I believe that Johannsen accepted a similar constraint in practice, though not Bateson's views about how it was to be met. As we shall see, Morgan and his colleagues explicitly rejected this constraint by 1915.

Morgan, like Bateson, was trained in embryology. Prior to his conversion to genetics late in 1910, he seems to have accepted a similar constraint on the adequacy of a theory of the gene. Here is a passage written in the middle of 1910 reflecting such a commitment:

"If Mendelian characters are due to the presence or absence of a specific chromosome [or part thereof], as Sutton's hypothesis assumes, how can we account for the fact that the tissues and organs of an animal differ from each other when they all contain the same chromosome complex... However important... the chromosomes are in transmitting the full quota of hereditary traits, we must be prepared to admit that the evidence is entirely in favor of the view that the differentiation of the body is due to other factors that modify the cells in one way or another. This consideration is, to my mind, a convincing proof that we *have to deal with two sets of factors – the common inheritance of all the cells to produce all the kinds of tissues and organs in the body, and the limitation of that property in the course of development*" ([37], my emphasis).

Like Bateson's, this commitment rests on the idea that a complete theory of hereditary factors must account for the ability of gametes to produce organized bodies with highly specific forms, differentiated properly under control of factors in the gametes. Once specific phenotypes such as this are admitted, given the physics and chemistry available at the time, it seemed highly unlikely or even impossible that chromosomal particles alone could do this job.

The contrast between this view and the position of the Morgan group a scant five years later is striking.

'Transmission genetics' is the traditional name for the domain of the Morgan group's greatest accomplishments. It focused primarily on our first group of questions: how are genes duplicated and transmitted across generations?

The group managed to develop unified, if incomplete, answers to these questions and to approach other questions on our list. As good pragmatics, they set aside and officially justified ignoring many other questions about genes, including the one on which Morgan focused in the previous text. Witness this striking passage, perhaps intended as a direct reply to Bateson, from the *Mechanism of Mendelian Heredity* (originally 1915), the textbook that established orthodox transmission genetics:

“It is sometimes said that our theories of heredity must remain superficial until we know something of the reactions that transform the egg into an adult. There can be no question of the paramount importance of finding out what takes place during development. The efforts of all students of experimental embryology have been directed for several years toward this goal. It may even be true that this information, when gained, may help us to a better understanding of the factorial [i.e. gene] theory – we can not tell; for a knowledge of the chemistry of all of the pigments in an animal or plant might still be very far removed from an understanding of the chemical constitution of the hereditary factors by whose activity the pigments are ultimately produced. However this may be, the far-reaching significance of Mendel’s principles remains, and gives us a numerical basis for the study of heredity. Although Mendel’s law does not explain the phenomena of development, and does not pretend to explain them, it stands as a scientific explanation of heredity, because it fulfils all the requirements of any causal explanation” ([38], pp. 280–281).

This quotation is the last paragraph of a chapter meant to defend the adequacy of the chromosomal theory’s account of ‘factors’ (genes). The striking claim that the chromosomal theory provides a causal explanation of adult characters in the absence of any explanation of the phenomena of development was written in full knowledge of Bateson’s criticisms, articulated sharply 2 years earlier. That claim illustrates the extent to which the Morgan group set aside legitimate questions about what genes do that fell outside their research program. This fact demonstrates how thoroughly they restricted the phenotypes of concern to the static products of developmental processes. Only by restricting in this way the phenotypes with which they dealt, could they hold, as they did, that they had met “the requirements of any causal explanation”.

Let us take this story forward one more step, to Goldschmidt’s *Physiologische Theorie der Vererbung* of 1927 [39]. Goldschmidt starts by setting forth a general account of the theory of heredity (*Vererbungslehre*). He begins with sections on the general assumptions that should be granted regarding the relation of the gene theory to the theory of heredity as of the mid-1920s. He explicitly agreed with Bateson and Johannsen that the theory of heredity must provide an account of how the genes present in the zygote direct the normal and abnormal processes that yield adult forms. But, unlike them, he accepted the evidence for the linear ordering of particulate factors on chromosomes as decisive. After a very clear brief exposition of the fact that

one can detect genes only in those cases where there are at least two alleles with distinct effects, he argues that there almost certainly are additional genes that have no detectable alternative alleles. For example, if there were alternate alleles affecting the success of the first cleavage of a zygote in yielding two daughter cells, we would not be able to discover the ‘defective’ alleles since any egg carrying them would be inviable. Students of development know many cases in which genes direct vital pattern-forming processes. Cleavage, itself, is such a process. Thus, it is reasonable to suppose that there are additional genes, which may or may not be located on chromosomes (a matter Goldschmidt considered relatively unimportant), and every reason to suppose that they are particles of much the same sort as the genes we already know.

All of this sets up his alternative to the stances of Bateson in 1913 and the Morgan group in 1915:

“Another way of stating the fact of heredity is to say that there must be something in the germ cells whose presence governs [*bedingt*] the exact repetition of all the events of development that had already led to the adult parent. It is a major accomplishment of science and an important stride for knowledge to have proven that this *something* has the form of a unitary material particle, the gene, that remains unchanged from cell division to cell division. [Later in the chapter, he indicates that the ‘something’ could be many such particles.] The nature [*Wesen*] of heredity first becomes clear when we can form a conception of how the genes that are present at the beginning [i.e. in the zygote] can intervene to determine [*bestimmend eingreifen*] the process of development. That they are present and that they intervene has been shown by the gene theory. The next step that must be taken on the way to a theory of heredity, is to learn *how* they intervene” ([39], p. 8).

Thus Goldschmidt agrees that Bateson’s constraint on an adequate theory of heredity was sound. We do not have a full-fledged theory until we have an account of how hereditary factors affect, control, or specify development. But Bateson was wrong to hold that this constraint undermines a Mendelian theory of particulate genes. Rather, the gene theory à la Morgan is a step along the way, but cannot by itself amount to the entire theory of heredity.

The moral I draw from this mini case study is that Bateson, Morgan, and Goldschmidt all derived their criteria of adequacy for definitions of the gene and for theories of heredity from consideration of the phenotypes they thought required explanation. What other option was there?

It is not hard to show that during the first couple of decades of Mendelian genetics there were attempts to answer the other basic questions on our list and that they, too, impinged on the criteria of adequacy for a theory of the gene or of heredity. Because of space limitations, I will mention in passing only one more example, concerning how genes act. As early as 1903, Cuénot [40] suggested that the genes affecting pigment formation in mice alter either a chromogen or an enzyme such as tyrosinase, the

role of which in forming melanic pigments had been studied by others. More widely known is Garrod's account of 1908 [41], according to which inability to produce specific enzymes, inherited in a Mendelian manner, is responsible for albinism, alkaptonuria, and other inborn errors of metabolism. Garrod attempted to follow up in cooperation with geneticists and biochemists, but these efforts were stillborn. Still, both men implied that an adequate theory should make clear how genes act to control the presence, formation, activation, structure, or availability of enzymes. This illustrates, once again, the interplay between the phenotypes explored and the attempts to develop research programs that would yield an answer to one of the basic questions on our list.

5. Disciplines, research programs, and *problématiques*

Our findings about the importance of the choice of phenotype in identifying genes illustrate a feature typical of work in the first half century of genetics – a feature that is still problematic and of great importance in functional genomics today! A long-term dialectic characteristic of the discipline was set off by the fact that different research programs employed conflicting assumptions. This dialectic stimulated attempts to achieve a generally satisfactory account of the nature of the gene, i.e. to produce a coherent set of answers to all of the groups of questions listed above. In pursuing particular programs of research, geneticists often set aside, at least for a time, the issues and constraints derived from work on the other questions and phenotypes. This was necessary to develop specialized investigative tools and organisms particularly suited to their questions. On the influence of experimental organisms generally, see [42] and on the special case of *Drosophila* [43]. For a more general perspective on choosing “the right tools for the job”, see [44], and on the importance of experimental systems [45]. It is hard to overestimate the practical value of restricting attention in this way, for it fostered the intensive development of experimental tools and close cooperation – or competition – with biologists in the relevant neighboring disciplines. But such narrowing of the field of focus generally brought about a reaction from other geneticists, committed to alternative visions of the gene.

Scientists are opportunists, and this was a natural way of proceeding in the face of a tangle of problems as difficult as the ones posed at the inception of genetics, especially given that most of the problems were beyond the reach of available experimental techniques. By isolating particular questions, geneticists could adapt or appropriate new tools and concepts, drawn from whatever sources, whenever they appeared likely to contribute to the solution of those particular questions.

The double character of genetic research arose because the groups of ‘obvious’ questions all concern the same putative objects – genes. From 1900 to 1950, pursuit of

different questions on our list produced conflicting views about the nature, properties, and behavior of genes. Individuals who crossed over from one set of questions to another or who, like Goldschmidt, had a synthetic turn of mind were repeatedly faced with the need to reconcile divergent claims about the nature and action of genes. Thus the ‘problem of the gene’ became an overarching, and extremely difficult problem that never disappeared totally from sight.

A brief sketch of the social structure of the discipline of genetics will sharpen this account of its dual character. The word ‘discipline’ is easily misunderstood here. Sociological markers suffice to indicate roughly what I mean. Characteristically, scientific disciplines are built around journals, international meetings, academic departments, a network of specialists, specific funding sources and patrons, specialized vocabularies, and specific investigative technologies and protocols. Some disciplines, e.g., protozoology, are delimited in terms of the objects studied (as, too, are various branches of agricultural genetics). Other disciplines, e.g., genetics, are delimited by an overarching topic or interlocking group of problems. Such markers as these enable us to characterize the content or aims of the discipline.

Genetics very quickly reached the status of a discipline. The third international congress took place in 1906. (There was no first or second; the President of the Third International Conference on Hybridisation and Plant Breeding, William Bateson, who had himself coined the term ‘genetics’, persuaded the relevant committees to rename that congress after the fact.) By 1915 the basic terminology and many techniques were established. There were laboratories, journals, a well-established network of self-identified geneticists, ongoing apparatus to maintain the series of international congresses, a Kaiser Wilhelm Institut, professorial appointments, agricultural field stations, and much more. And the problem of the gene (among others) provided the intellectual glue that justifies counting it as a discipline.

The dual character of genetics is clarified by distinguishing between ‘*problématiques*’ and ‘research programs’, although, again, the labels may be misleading. I use ‘*problématique*’ as the more general term. Each group of questions on our list generates a *problématique*. Thus, Bateson and Goldschmidt both focused on the question as to how genes control or produce adult traits; to this extent they shared a *problématique*. Bateson did not develop techniques or protocols with which to develop a consistent long-term program of work for this purpose; he had no research program with which to attack it. Goldschmidt, in contrast, organized his work on the secondary sexual characters of intersexes of *Lymantria dispar* as a means of attacking this problem [39]. In 20 years of studies, he developed detailed evidence to show that differences in the rates of specific reactions controlled by particular genes governed a balancing mechanism affecting the formation of male versus female secondary sexual charac-

ters. This illustrates the use of a program of research to address a *problématique*.

The major advances – and failures – in the first half century of genetics stem from particular programs of research. Typically, these focused on special cases bearing on one or two groups of questions on our list. Typically, they drew heavily on the work of some other discipline, as the Morgan group drew on cytology [46]. As should now be obvious, cross-disciplinary influences deeply affected researchers' choices of phenotype to investigate and, with that, their commitments about the nature of genes. In general, people with highly developed research programs became deeply wedded to the assumptions that allowed them to shut out conflicting perspectives and evidence and to bypass problematic issues with which they were not equipped to deal. As their program flourished, it supplied their intuitions, their standards for solving experimental problems, and numerous core beliefs about what genes are and/or how they work. When a program of research focused on one or more basic questions and met with strong success (as happened especially to the Morgan group), that line of work tended to result in rapid production of a large amount of research, eventuating in the formation of a major subdiscipline. Nonetheless, genetics as a whole was not unified by any single program of research or subdiscipline. Two reasons for this are worthy of note.

First, no research program came near to solving the problem of the gene. All of them concentrated on one or two of the groups of questions on our list and either offered no answer at all to other questions or produced results that seemed incompatible with alternative answers to those questions. Second, theoreticians provided striking characterizations of the features of the gene (or the genetic material) that made it clear that the holy grail of solving the problem of the gene was worth an enormous amount of work. For example, H.J. Muller (e.g., [47, 48]) spelled out very general features of the behavior of genes that would have to be explained by any full solution to the problem of the gene. Genes are 1) autocatalytic (i.e. reproduce exactly), 2) heterocatalytic (i.e. somehow direct the formation of other materials or products, distinct from genes) and 3) mutable *while retaining properties (1) and (2)*. No known material had these properties, yet there was no way around ascribing all three properties to genes. Thus, successful research in genetics not only offered great practical benefits, but also promised to solve some very fundamental scientific problems. This provided an incentive to reconcile the conflicting insights deriving from particular research programs.

We cannot examine here the narrower programs of research that addressed different questions from our initial list. A fuller account of the dynamics of the development of genetics would demonstrate the way many such programs forged connections with other disciplines, but also produced results that called for regimentation under a coherent solution of the problem of the gene. Only with this fuller account would it be clear how widely the

problem of the gene ramified into theories across the whole range of biology.

6. Conclusion

The dynamics of development in Mendelian genetics is quite different than is suggested by leading accounts of scientific change. For example, genetics as described above does not come anywhere near to sharing a Kuhnian paradigm [49]. Indeed, Kuhn's term as used nowadays does more harm than good, for, on the picture I have developed, even those who work in a well-focused research program do not share anything quite as rigid as a Kuhnian paradigm. Consider the Morgan group: although its members were deeply committed to a large number of practices and views, the practices built on comparison of cytological findings about chromosomes and genetic findings about patterns of inheritance were deployed in investigations of development, populations genetics, and the material of the gene. Cytological findings were used to correct genetic claims and vice versa, as well as to confirm key hypotheses. By crossing disciplinary barriers, it was possible to develop machinery for correcting errors. That process, far from automatic, involved scrupulous matching of findings from each domain to detect discrepancies and to support, refine, or correct the findings of the other domain [46]. Even though Kuhn eventually retreated from discipline-wide paradigms to research program-wide paradigms, his account of the fixity of the tacit theoretical commitments built into a paradigm does not fit the actual structure of work in the Morgan group.

As a second example, the research programs described in this paper do not exhibit the structure put forward by Imre Lakatos's in his *Methodology of Scientific Research Programmes* [50]. A Lakatosian research program has a hard core of unchangeable assumptions – unchangeable because of the decisions and practices of the adherents of the research program – and a protective belt of hypothesis and practices that direct the arrow of experimental refutation away from the hard core. It is of course true that unfavorable results do not immediately defeat a fundamental theoretical claim; the problem may lie with boundary conditions, impurities, or erroneous secondary hypotheses. But adherents of research programs like the Morgan group and Goldschmidt do not work with a definitively established hard core of commitments such that to abandon any one of them is to abandon the research program. Goldschmidt's indifference in 1927 (when he was a good Mendelian!) as to whether all genes are located on chromosomes illustrates the compatibility of the Morgan group's findings with a less chromosome-centered Mendelian doctrine. Goldschmidt's abandonment of particulate genes at the end of the 1930s did not require abandonment of his research program. The Morgan group's recognition of the presence of genes in chloroplasts conflicted with some of their deepest convictions and seriously altered the practices of chromosomal genetics. Nonetheless, it is simply wrong to claim that acceptance of

chloroplastic genes and the limited amount of cytoplasmic inheritance thus entailed put an end to the Morgan group's research program or so transformed it as to make it into a new research program.

I close with a brief positive account of the dynamics of discovery in genetics 1900–1940. Mendelian genetics was held together – somewhat loosely – by the commitment to the idea that there really are Mendelian genes and that there must therefore be a coherent and consistent set of answers to basic questions about those genes. It was recognized that some questions might have to be transformed if they could be shown to rest on false assumptions. But the need remained urgent to develop a coherent and consistent account of what genes are, where they are to be found, what they are made of, and how they act. In order to answer those questions, given the limited technical and theoretical tools available before 1950, it was necessary to separate questions into the smallest, most tractable bits possible and to exploit all possible investigative tools as they became available. Progress on particular questions came episodically, in powerful and compelling bursts. Early on, breeding techniques, intimately connected with the interests of agriculture, fancy breeding, and, yes, eugenics, provided the most important information. The connection with wealthy farmers, breeders, and proponents of eugenics provided important sources of funding and patronage that made fairly large research programs possible and helped to shape them. Such support also provided the margin for more esoteric research. As new technologies (e.g., radioisotopes and ultracentrifugation), mathematics (cf. population genetics) links to other disciplines and their experimental tools (cf. physi-

ological and biochemical genetics), organisms (cf. *Drosophila*, yeast, *Neurospora*, etc.) were exploited, new bursts of activity altered the landscape. There were associated with new research programs that, if they flourished, pulled genetics in new directions. Much of the esoteric research in these domains began as an attempt to remove the conflicts that arose from discrepant answers to the basic questions on our list. Geneticists were forced to work opportunistically, working as amateurs in other domains in order to appropriate new experimental technologies and to link their theoretical and experimental work to that in other biological theories and disciplines.

As different research programs became established, the differences in their accounts of the gene only heightened the conflicts. The resulting disagreements were a source of continuing tension and a spur to research. Conflicts over fundamentals forced theoretically inclined geneticists to attempt to reintegrate findings whenever a major program of research made significant progress. Thus, the internal dynamics of Mendelian genetics forced geneticists into ever-widening domains and into the interdisciplinary research that helped propel them toward the molecularization of genetics, which took hold after World War II.

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