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Mendel's Impact

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Argument

I wish to propose that the history of genetics reflects the history of the concept of reductionism in the life sciences. Reductionism is the thesis that explanation of laws or phenomena in one realm by those of another realm are always likely to be successful as explanations. By 1900 reduction of biology to the laws of chemistry and physics was not self evident: Although bottom-up preformationist explanations were largely inadequate for development, top-down epigenetic hypotheses often adopted metaphysical assumptions. Similarly, top-down theories of evolution as dependent on the accumulated impact of the past confronted those of bottom-up notions of fitness of specific traits that are relevant for future evolution. Mendel's 1865 *methodological* reductionist study of inheritance of traits was embraced in 1900 as evidence for reduction at the *conceptual* level. With the achievements of research of the mechanisms of inheritance, genetics became increasingly genocentric in its explanatory arsenal of development, and accordingly it was in conflict with the top-down, life-as-organized-systems' notions of embryology. Similarly, evolution was conceptually reduced to changes of gene-frequencies in populations. It was, however, precisely the increasing attempts to ground the bottom-up approach at the molecular level that eventually pushed conceptual reductionism to its crisis. Modern developments of molecular and computational methods finally forced, or allowed, researchers to apply *bottom-up methodologies to top-down systems' analyses*.

The name of Johann Gregor Mendel (1822–1884) is associated in the minds of most of us with the founding of the science of genetics, when in 1865 he presented to the meeting of the Brünn Natural History Society his results of hybridization experiments and their interpretation. But Mendel was primarily a monk and a plant breeder at the Augustine Monastery in his home town Brno (Brünn), and as noted by Curt Stern (Stern and Sherwood 1966, v), "Mendel's triumph was a lonely one." Neither his audience nor the readers of his reprints appreciated the significance of his achievements. Although Mendel believed that his day would come, he did not act to encourage this to happen (see Orel 1996). Mendel's work was recognized in 1900. But, what was the relation of Mendel of the 1860s to the Mendel of the science of genetics that emerged at the beginning of the twentieth century: To what extent was the science of genetics of the twentieth century the intellectual child of the breeder monk in Brno? According to Stern,

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> The observations and their analysis which Mendel supplied have indeed led far. Without a break in intellectual continuity they became the Mendelism of the early years of this century, joined with the study of chromosomes to expand into the cytogenetics of the next decades, took on new meaning when the biochemical and developmental activities of Mendel's "cell elements" came into the foreground of investigations, and remain conceptually one of the bases of the most advanced contemporary molecular genetics. (Stern and Sherwood 1966, vi)

Others, however, questioned the extent to which Mendel the founder of modern genetics and Mendel the breeder-monk were the same, or as challenged by the historian of genetics, Robert Olby: "Mendel no Mendelian?" (Olby 1979). Was the breeder-monk "concerned with the behavior of hybrids and not with the inheritance of characters per se" (Monaghan and Corcos 1990, 289)? In short, are the foundations of the science of genetics of the twentieth century rooted in of the hypotheses of Johann Gregor Mendel?

I wish to maintain that Mendel's 1866 paper was indeed the founding treatise of the science of heredity *as we know it today* in that it (a) established the methodology of genetic analysis by inferring hereditary *Faktoren* from discrete traits, and (b) did not commit his *Faktoren* theory to the nature of these factors. It was the combination of these two notions that allowed research of inheritance to become the science of genetics and to struggle for its independence (Falk 1995). Yet, I insist that genetics, as the science of heredity that was always involved in theories of evolution, was never divorced from the notions of development. Rather, we have been witnessing in the nineteenth and the twentieth centuries a full cycle, from a holist view of heredity as an aspect of development and evolution that inevitably fell back on metaphysical assumptions, to the higher level of a rational though reductionist view of hereditary factors of development and evolution, and then back to a holistic perspective of heredity at the level of systems' analysis of development and evolution. Thus, I submit that the renewed amalgamation of the disciplines of genetics, evolution, and development towards the end of the twentieth century may be conceived as another triumph of Mendel's impact.

Genetics: Coming of Age of Heredity

Mendel's direct impact on the science of genetics of the twentieth century, I wish to propose, was introducing a reductionist agenda to the research of heredity. This notion of Mendel, I believe, was based primarily on a deep religious conception of the world as governed by laws of nature formulated in numerical principles (Falk 2001a). As shown by Monaghan and Corcos, Mendel had gone through all steps of an empirical scientist of the time, including "empirical laws . . . best sought for in experiments yielding quantitative relationships which can be formulated in symbolic

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terms and interpreted through existing mathematical principles." Furthermore, "given the empirical laws that state in concise quantitative, symbolic form what happens," an attempt was made to provide a mechanism or process [that] . . . must draw upon and be consistent with contemporary knowledge in the field." Thus, "Mendel's work was the creation of a mathematically precise science of hybridization modeled upon the physical science" (Monaghan and Corcos 1990, 289). Already in describing the design of his experiments Mendel stated his explicit reductionist methodology, employed in the search of universal laws of nature:

> It was the purpose of the experiment to observe these changes for each pair of differing traits, and to deduce the law according to which they appear in successive generations. Thus the study breaks up into just as many separate experiments as there are constantly differing traits in the experimental plants. (Mendel, in Stern and Sherwood 1966, 5)

Mendel, however, bequeathed to the science of genetics another notion, beyond that of the employment of a reductionist research method, namely, *he did not introduce a particulate material notion into the study of heredity* – he talked of *Faktoren*. As pointed out by Gayon (2000, 71–73), it was Darwin who rejected the prevalent notion of *hereditary force* and promoted a notion of material particles, *gemmules*. Contrary to Monaghan and Corcos's claim that Mendel's objective was merely to find the empirical laws that describe the formation of hybrids and the development of their offspring over several generations, and that "he never developed what might be called the sixth level of abstraction . . . the proposal that the reason why a certain cell was of certain type, *A* or *a*, was that particulate determiners were present in the cells" (Monaghan and Corcos 1990, 290), he did develop an explicit theory of inheritance stated in the formulation of universal laws (Falk and Sarkar 1991). The monk Mendel did not need to confine his universal theory of inheritance to particulate material factors.

When Hugo de Vries (1848–1935) in 1900 found support in Mendel's experiments of the 1860s for his own hypothesis of *intracellular* development and evolution, he associated Mendel's *Faktoren* with particulate *pangenes*. De Vries, however, was primarily interested in backing up his own hypothesis rather than in establishing pangenes as foundations of a theory of particulate heredity. Notwithstanding, his role in promoting Mendel's insight was crucial, though indirect. To a large extent, the history of the science of genetics in the twentieth century may be viewed as that of the confrontation of Mendel's "factors" with that of de Vries' "particles."

Although the younger Carl Correns (1864–1933) was less interested in the ambitious formulation of universal laws of nature, his studies of the physiological properties of the traits – or rather in the "anlage thereof" in "intervarietal hybrids" – led him to identify Mendel's factors with his anlagen. Unfortunately, he did not grasp in due time the potential of Mendel's work as the dawn of a new science of heredity. He related that he was aware that he "had found *something new*," but added "that Mendel's Law of segregation cannot be applied universally," and accordingly, he "did not consider it

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necessary to establish" his priority (Correns 1900, in Stern and Sherwood 1966, 120; see also Rheinberger 2000).

William Bateson (1861–1926) never claimed to have had discovered either the Mendelian ratios or their explanation. Yet it was he who conceived of Mendel's experimental work as a founding contribution to the new research discipline of heredity and variation, which in 1906 he called *genetics*. Contrary to de Vries who superimposed his notions of pangenes' function on the Mendelian factors in the service of his theory on the Origin of Species by Mutations (*Die Entstehung der Arten durch Mutation*, de Vries, 1902–03, II, xii), Bateson like Correns was interested in the experimental discovery of the nature of these factors of inheritance and their role in evolution and in development. It must, however, be kept in mind that all adhered to notions of material preformationism that did not discriminate conceptually between the factors for traits and the traits proper: This was obvious from their respective treatment of the concept of dominance: For de Vries dominance and recessivity were integral, lawful parts of his particulate theory of trait-differentiation by activation-inactivation of latent pangenes (see Stamhuis 2003; Stamhuis et al. 1999). Correns and Bateson treated dominance and recessivity simply as instruments for the study of factors becoming traits: Correns considered it a *physiological*, "vegetative," threshold phenomenon of trait-development, whereas Bateson formulated a *material* Presence-Absence Hypothesis of the Mendelian factors to explain the dominance and recessivity of the traits (see Falk 2001b; Rheinberger and Müller-Wille 2006).

It was eventually Wilhelm Johannsen (1857–1927) who laid a new foundation for the examination of the nature of the Mendelian *Faktoren* when he formally introduced in 1909 the distinction between the phenotype and the genotype, or between the "unit character" and the *gene*. Johannsen was most careful not to attribute any explicit material meaning to his gene-concept (Johannsen 1909). His gene was simply an intervening variable. However, with the establishment of the Chromosomal Theory of Inheritance by Thomas H. Morgan (1866–1945) and his students, the Mendelian units of inheritance became hypothetical constructs, and for at least one of his students, Hermann J. Muller (1890–1967), the genes were discrete material entities, the atoms of inheritance, the physical-chemical properties of which he set out to study. The establishment of DNA as the material basis of heredity and that of the molecular model of its organization, which for a short time appeared to settle the issue of Mendel's *Faktoren* as discrete material unit of heredity, soon led to bewilderingly complex notions of the nature of *the gene*, and the nature of the reducible unit of heredity (Falk 1986).

Notwithstanding, in the footsteps of Mendel, who heuristically sublimed the details of the characters that he judiciously *selected* for his experiments on transmission between generations, geneticists could develop techniques for the study of transmission mechanics, independently of the physiological or developmental effects of traits. Correspondingly, whenever investigators attended the specific problems of heredity in development and evolution, these were reduced – methodologically and eventually conceptually – to those of discrete gene effects. Starting with Bateson's

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Presence-Absence hypothesis of dominance (Bateson [1905] 1928), through Muller's interpretation of dominance as precision of genetic functional adaptation (Muller 1950), to Beadle and Ephrussi's study of specific discrete gene-products that culminated in the one-gene – one-enzyme thesis (Beadle and Ephrussi 1936; Beadle and Tatum 1941), and to the formulation of the New-Synthesis of evolution in terms of populations' gene frequencies (see Provine 1971), geneticists inferred rules of development and of evolution in which the gene provided "a kind of inertia principles" against which discrete effects could be measured (Rheinberger and Müller-Wille 2006).

Significantly, at the turn of the twenty-first century, Elof A. Carlson re-examines *Mendel's Legacy* of the methodology of inferring hereditary *Faktoren* from discrete traits (Carlson 2004), while Lenny Moss wonders *What Genes Can't Do* (Moss 2003), and Falk views *The Gene – A Concept in Tension* (Falk 2000b). Molecular biologists avidly debate the number of *genes* in the genome of various organisms, but there is no consensus to what stretches of the DNA strand they refer, and current findings (e.g., in micro-RNA research) further stress that the units of inheritance are *factors* rather than *particles*.

Genetics: Inheritance with Development

Reduction involves the explanation of laws or phenomena in one realm by those of another. Reductionism is the thesis that reductions between two realms are always (or, at least, are always likely to be) successful as explanations. I wish to differentiate between methodological reductionism and conceptual reductionism.

Methodological reductionism is the belief that empirically following single (experimental or observational) variables (other variables being kept constant or randomized) is the effective design to bridge realms.

Conceptual reductionism assumes that phenomena may be reduced to a component or components at a more basic realm, that individually or interactively bridge the phenomena at the higher realm.

The distinction is one between explanation and resolution. Methodological reductionism may be identified as an epistemological statement, whereas conceptual reductionism is essentially an ontological statement (Sarkar 1998, 17ff; see also Nagel 1961; Schaffner 1976).

Modern science has been *methodologically* reductionist, ever since Galileo introduced the study of one variable at a time, by keeping all other variables as much as possible constant (or, at least, let the other variables vary randomly with respect to the variable studied). It became also increasingly Cartesian, or *conceptually* reductionist.

The achievements of reductionist methods and conceptions in physics, and eventually also in chemistry, encouraged researchers to extend reductionism to living organisms. But the study of life in the eighteenth century was demarcated at the outset from physics and chemistry as immanently non-reducible to the laws of physics and

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chemistry. In spite of nineteenth-century biologists' inroads in extending reductionism to the life sciences (Lenoir 1982), it seemed that life remained immune to complete conceptual reductionism. Something else – metaphysical – was needed, whether it was Kaspar Friedrich Wolff's *vis essentialis,* Johann Fiedrich Blumenbach's *Bildungstrieb*, Carl Nägeli's *Vervollkommnungskraft,* Theodor Eimer's *Orthogenesis,* or Hans Driesch's *Entelechy*. Eventually it culminated in Niels Bohr's search for special laws of physics expressed only in living systems, or in the modern theories of complexity. The wish to reduce living beings to systems that may be completely explained bottom-up, countered the recognition that living beings *are* the fundamental entities that should be explained top-down in order to unravel the properties of their components.

The three major conceptual revolutions in the life sciences of the nineteenth century, the cellular theory (1838–1839), the theory of evolution by natural selection (1859), and the theory of *Faktoren* inheritance (1865), all reflect the craving for adopting reductionist methodologies in explanations of living systems, with no commitment to reductionist conceptions of resolving biology into physics and chemistry.[1]

Of the three, Darwin's (1809–1882) hypothesis of *The Origin of Species by Means of Natural Selection* was actually a top-down theory. But Darwin's juxtaposition of the organism *versus* its environment, independently of what the organism "wants" or needs – contrary to conceptions up to and including the Lamarckian hypothesis of the organism *in* its environment – inserted a conspicuous reductionist element into his hypothesis, which was fostered by his followers. Although Darwin repeatedly tried to back out of this methodology of the organism-environment segregation, the reductionist aspect of Darwinism, of "Nature *versus* Nurture," as phrased by Francis Galton (1822–1911) in 1865, was firmly established once formulated by August Weismann (1834–1914) in the germ-plasm theory of heredity (Weismann 1893).

Matthias Schleiden (1804–1881) and Theodor Schwann's (1810–1882) reductionist theory of the cell as the universal entity of living systems gained its success with Rudolf Virchow's (1821–1902) 1855 doctrine of *omnis cellula e cellula*.

Only Mendel's reductionist notion of discrete factors of heredity had to wait until the turn of the twentieth century to gain recognition: Heredity and development were intimately confounded, and it was in the field of development *with* inheritance in which the reductionist and holistic approaches confronted each other most directly. Wilhelm His (1831–1904) and Wilhelm Roux (1850–1924) introduced the mechanics of development (*Entwickelungsmechanik*) largely in the hope of repeating the achievements of the reduction of physiology to physics and chemistry:

> Developmental mechanics is the doctrine of the causes of organic forms. Form represents the most essential attribute of the organism. . . . In accordance with Spinoza's and Kant's definition of mechanism, every phenomenon underlying causality is designated

[1] In this sense the commitment of physiologists was different: Theirs was a conceptual reduction, as has been highlighted by introducing the term biochemistry in the late nineteenth century.

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> as a *mechanical phenomenon;* hence the science of the same may be called mechanics. Since . . . physics and chemistry reduce all phenomena, . . . to movement of parts, . . . the words "developmental mechanics" agree with the more recent concepts of physics and chemistry, and may be taken to designate the doctrine of all formative phenomena. . . . In so far, however, as forces or energies are only known by their *effects*, . . . the problem may be defined as the *ascertainment of the formative modi operandi*. (Roux [1894] 1986, 107–108; emphasis in original)

Yet, as Roux himself was conscious of, even if a bottom-up mechanical methodology was imperative, the conceptual reduction of development was more problematic and controversial:

> . . . developmental mechanics must from the start be guided by the conviction *that organic structure is mainly due to the operation of components which at present are so complicated as to exceed the limits of our observation*. . . . Although according to our immediate conception of the matter, even these components depend in the last instance on inorganic *modi operandi*, nevertheless *the complexity of the composition lends them attributes which often differ so widely from those of inorganic modi operandi* that they are not only very *dissimilar* but even *appear to contradict* in part functions of these same inorganic *modi operandi*. (Ibid., 111; emphasis in original)

For embryologists the issue of the mechanism of development became part of the discussion of preformationism versus epigenesis, i.e., of the extent of the immanent, inheritance of developmental processes. Although a long way from the old notion of Hartsoeker's (1694) homunculus, preformation, or the bottom-up view of development as the sum total of the physical and chemical properties of its building blocks was the notion that dominated. Those who adhered to the opposite conception of epigenesis, which conceived of the organism as the frame of reference that assimilated the environmental, including the inherited cues in development, could not construe it in terms of additively reducible physico-chemical terms (as preformationist *hoped* was feasible). As noted, epigenesis repeatedly implicated scientists, sometimes inadvertently, with *sensu stricto* meta-physical notions, such as *Bildunstrieb* or *Entelechy*, of development.

The predicament of the analytical biologist with conceptual reduction, when confronted with his experimental results obtained in the best tradition of the reductionist methodology, was presented most eloquently by Edmund B. Wilson in his 1893 lecture at the Marine Biological Laboratory in Woods Hall:

> Many leading biological thinkers now find themselves compelled to accept a view that has somewhat in common with the theory of prae-formation . . . Every one of [the] hereditary characters is . . . represented by definite structural units in the ideoplasm of the germ cell, which is therefore conceived as a kind of microcosm, . . . [T]he so-called mosaic theory of Roux and Weismann . . . is essentially a whole arising from a number of independent self-determining parts, . . .

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> [Yet, a] more decisive result was reached in 1891 by Driesch, . . . [which] the writer repeated . . . and found that . . . [t]he isolated blastomere behaves from the beginning, like an entire ovum of one-half or one-fourth the normal size. . . .
>
> These facts are obviously a serious blow to the mosaic theory, and the efforts of Roux and Weismann to sustain their hypothesis in the face of such evidence only serve to emphasize the weakness of their case. (Wilson [1893] 1986, 69–72)

The problem was a conceptual one, rather than one of methodological particularization. It is here that Mendel's accomplishment, of judiciously selecting appropriate markers for his experiments in the 1860s, applying the reductionist *methodology* to the inheritance, without making an explicit statement on the *conceptual* problem of development, is fully paying off. This was noted already in 1902 by Udny Yule (1871–1951):

> The experimental plants must, Mendel states . . . "possess constant differentiating characters." . . . The races for crossing were thus chosen with the greatest care and patience so as to be absolutely distinct; an *A* individual mated with an *A* never producing *a*'s, nor vice-versâ, for, as I understand, the whole period of ten years (two years of preliminary trials and eight years of experiment). (Yule 1902, 222–223)

Contrary to Mendel, who *selected* his unit-characters, for preformationist Bateson, once he adopted the notion of units of inheritance, Mendelian segregation *defined* unit-character: To the extent that the morphologist's or physiologist's unit character did not agree with those of Mendelian segregation units, the former were not really "unit characters," but rather complex characters. Thus, Mendelian segregation became for Bateson a device to assess spurious morphological unit characteristics, such as in the case of chickens' comb morphology; The "walnut" comb was a compound of two unit-characters, the "pea" comb and the "rose" comb because it segregated as a dihybrid (Schwartz 1998; Schwartz 2002).[2] Indeed, much of the dispute between the Mendelians led by William Bateson and the Biometricians led by Karl Pearson may be traced back to the fact that both sides conceived the Mendelian factors as preformed

[2] William Bateson's ignoring any chromosomal association with Mendelian factors has recently been explained by Patrick Bateson as being due to his irritation about "the glibness of the explanation offered for the role of chromosomes. The chromosome was portrayed not simply as a structural site of the gene but . . . was treated as the pre-formed version of the character influenced by the gene on that chromosome" (Bateson 2002). Reviewing Morgan's *Mechanism*, William Bateson wrote that "It is inconceivable that particles of chromatin or any other substance, however complex, can possess those powers which must be assigned to our factors. . . . The supposition that particles of chromatin, indistinguishable from each other and indeed almost homogenous under any known test, can by their material nature confer all the properties of life surpass the range of even the most convinced materialism" (Bateson 1916). Bateson was looking for a more sophisticated material preformationism: In response to the question how Bateson missed the tie-up of linkage phenomena with the chromosomes, his colleague, Punnett, answered: "The answer is Boveri. We were deeply impressed by his paper 'On the individuality of the chromosomes' and felt that any tampering with them by way of breakage and recombination was forbidden" (Punnett 1950).

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unit-characters. Thus, in hybridization experiments performed by Darbishire with mice, unexpected variations in the trait of fur color, contrary to the preformationist principle of dominance that predicted uniformity of color for unit characters in the F_1, were taken by Biometricians as evidence against Mendelian determinism (Ankeny 2000, 328). Similarly, William Castle's explanation of the variation in color-patterns of hybrid rats by a model of allele-contamination in heterozygotes (Castle 1906) was based on a preformationist notion that did not distinguish between traits and the factors for traits.

> My own experimental studies of heredity, begun in 1902, early led me to observe characters which were unmistakably *changed* by crosses and so I have for many years advocated the view that the gametes are not pure in the sense expressed by Bateson. (Castle 1919, 126; emphasis in original)

Notably, Johannsen's resolution of the difficulty of the unit characters being preformed *Faktoren* stemmed from pushing the preformationist notion to its extreme: Johannsen was an essentialist typologist (Roll-Hansen 1978). From his top-down viewpoint, the essence was an Aristotelian genotype, the mundane, earthly appearance of which was the phenotype. By emphasizing the status of the genotype as the essential entity, Johannsen accepted the role in development of the environment and the circumstances in which the genotype developed, thus severing the Gordian link between the unit character and the hereditary factor.

> Sodann erkennen wir, daß der "Typus" im Quetelet'schen sinne nur eine *Erscheinung oberflächlicher Natur* ist, welche täuschen kann; erst durch weitere Untersuchungen wird entschieden, ob ein einziger oder mehrere biologisch verschiedene Typen vorhanden sind. Darum könnte man den statistisch hervortretenden Typus passend als Erscheinungstypus bezeichnen oder, kurz und klar, als "*Phaenotypus*." (Johannsen 1909, 123; emphasis in original)[3]

For Johannsen the genotypes are as constant as chemical elements, whatever the properties of the compounds these elements are involved in might be. It is important to note, however, that for Johannsen the major distinction was that between the *phenotype* and the *genotype*; his introduction of the "gene" was a bow to Mendel and Weismann, in spite of his typologist conception. From the perspective of one decade later he asserted:

> My term "*gene*" was introduced and generally accepted as a short and unprejudiced word for unit-factors . . . but originally I was somewhat possessed with the antiquated

[3] Thus we recognize that the "type" in the sense of Quetelet is only an *appearance of superficial nature*. This can be misleading. Only through further investigations is it decided whether a single type or numerous, biologically different types are at hand. Therefore one could appropriately denote the statistical prominent type as the appearance-type, or, shortly and clearly, as the "*phenotype*."

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> morphological spirit in Galton's, Weismann's and Mendel's viewpoints. From a physiological or chemico-biological standpoint . . . *there are no unit characters at all!* . . . We may in some way "dissect" the organism descriptively, using all the tricks of terminology as we please. But that is not allowed in Genetical explanation. Here, in the present state of research, we have especially to do with such genotypical units as are separable, be it independently or in a more or less mutual linkage. (Johannsen 1923, 136–137; emphasis in original)

Hence, by his insight Johanssen provided the framework that paved the way for the new science of genetics to become phenomenologically reductionist without being preformationist, or to adopt an "instrumental reductionism" without adopting a "material reductionism" (Falk 1986). This was crucial in the conversion of another ardent opponent of Mendelian preformationism, namely Thomas Hunt Morgan. Morgan repeatedly tried to maintain the distinction between methodological reductionism – which he accepted – and conceptual reductionism – which he tried to postpone, if not reject. Johannsen's distinction between the genotype and the phenotype allowed Morgan to adopt a chromosomal theory of heredity without being committed to developmental preformationism (see, e.g., Falk and Schwartz 1993). In 1910, opposing preformationism, Morgan asserted that "When we speak of the transmission of characters from parent to offspring, we are speaking metaphorically" (Morgan 1910). The metaphor was apparently resolved so that in 1934, in his book *Embryology and Genetics*, he asserted that "The story of genetics has become so interwoven with that of experimental embryology that the two can now to some extent be told as a single story." He even came up with an important model – not testable at the time – of development through differential activation of the constant hereditary entities, universally present in all somatic cells (Morgan 1934, 9–10). Notwithstanding, Morgan had to give way to the technical hurdles that this position put in his thinking (Allen 1978; Falk 1986), and Jane Maienschein deemed that in spite of consistent efforts he could not reconcile the old couple of embryology and genetics. According to her: "In the end, with his book *Embryology and Genetics* of 1934, he did not even find it profitable to try very hard" (Maienschein 1987, 92): The "and" in the book's title turned out to be more a dissociate- than an associate-conjunction.

The implicit distinction between the reductionist conception and the reductionist methodology, central to many students of the generation of Developmental Mechanics became, however, rather blurred among the students of the generation of the Chromosomal Theory of Inheritance. Thus, by the beginning of the second decade of the twentieth century, when the focus of genetic research moved from Europe across the Atlantic to the United States, and especially to Morgan's "Fly-Room," new lines began to be drawn: Contrary to the Central European research tradition driven by a strong philosophical worldview, whether holistic or reductionist (for a more extensive discussion, see Harwood 1987), the American tradition was more a pragmatic, methodological reductionism, which degenerated into conceptual reductionism.

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Confronted with the achievements of reductionist genetics of the Morgan school, Johannsen's appeal for a genotypic – we would call it nowadays, genomic – perspective, was to no avail:

> We are very far from the ideal of enthusiastic Mendelians, viz. the possibility of dissolving genotypes into relatively small units, . . . Personally I believe in a great central "something" as yet not divisible into separate factors. The pomace-flies in Morgan's splendid experiments continue to be pomace-flies, even if they lose all "good" genes necessary for a normal fly-life. . . .
>
> But however far we may proceed in analyzing the genotypes into separable genes or factors, it must always be borne in mind, that the characters of the organisms – their phenotypical features – are the reaction of the genotype in toto. The Mendelian units as such, taken per se are powerless. (Johannsen 1923, 139)

Obviously, Johannsen was increasingly alarmed by genetics becoming more and more conceptually reductionist or genocentric. Instead of characters being "markers" for genes, genes became entities "for" characters. Any attempts to maintain a top-down conception were marginalized.

The genocentric notion was very effective as long as research centered on the mechanisms of inheritance and the organization of the genetic material. Basically traits were selected for experimentation which, under laboratory conditions, trustfully allowed following the genotypic make-up, notwithstanding calls like Woltereck's (1877–1944) to pay attention to the norm of reaction of genotypes as a function of the environments with which they interact (Woltereck 1909). Similarly phenotypic deviations of the pre-determined genetic essences were dismissed by trivializing the variations as due to "penetrance" or "expression" of the mutants (see Falk 2000a). As Laubichler and Sarkar (2002) note, these concepts "are invoked when any simple relation between a specific genotype and phenotype break down."

Perhaps the most explicit conceptual reductionist was Herman J. Muller, who identified genes as the atoms of inheritance and variation, the physico-chemical properties of which should be elucidated. Nevertheless, Muller too was interested in the role of inherited factors in development (Falk 1997). But, as stressed by Allen "the strong emphasis on discrete and separable units interacting additively, as opposed to synergistically, posed serious problems for understanding developmental processes" (Allen 2002, 27). Non-genocentric notions, like Richard Goldschmidt's (1878–1958) top-down philosophy, just as Barbara McClintock's (1902–1992) genomic – sometimes mystic – conception, were politely but emphatically rejected. Significantly, however, Lewis Stadler's (1896–1954) conceptual holism yet methodological operationalism (Stadler 1954) was gracefully acknowledged.

In retrospect, in spite of the main research effort being directed in the first half of the twentieth century at the mechanics of inheritance, the involvement of geneticists in issues of development was not less intensive than that of the biologists in the

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late nineteenth century who insisted that heredity and development were inseparable (Maienschein 1987; Sandler and Sandler 1985). However, the study of the inherited aspects of development was now skillfully converted, along Mendel's reductionist notion, to problems of the function of individual genes in development of specific traits rather than that of organisms or germ-layers: J. B. S. Haldane (1892–1964) described the function of specific genes in the synthesis of antocyanines that determine the flower color in Pelargonium (Haldane 1954, 52–58) and Alfred H. Sturtevant (1891–1970) described the function of specific genes in directing the left or right coiling in the snail *Limmnea* (Sturtevant 1923).[4] George Beadle (1903–1989) and Edward Tatum (1909–1975) reduced the metabolism of the mould *Neurospora crassa* to that of a "one-gene – one-enzyme" relationship. They appropriately emphasized the direct line leading from Garrod's (1857–1936) "inborn errors of metabolism," which assigned malfunction to specific hereditary factors involved in metabolic pathways that cause certain human diseases, to their experimentally induced genetic metabolic failures in the bread-mould (Beadle and Tatum 1941).

Typical to such a gene-centered view of development is the problem of pleiotropy – the production by one particular mutation of apparently unrelated multiple effects: Assuming reduction to discrete particulate genes, could pleiotropy be genuinely "primary" – one gene producing fundamentally many products – or was it "secondary," according to which all the multiple effects of a gene could be reduced to a single effect (see Falk 2000a)?[5]

Notwithstanding, in spite of the urge for simplifying, reductionist methodologies, the awareness of the need to refer to the organism when discussing genes in development, remained constantly on the mind of students of inheritance and development. Based on his work on the pigmentation of the moth *Ephestia küniella*, Alfred Kühn (1885–1968) pointed out that our methodological experimental reductionism should not distract us from a conceptual holistic notion of the organism:

> [Our] apprehension of the expression of hereditary traits is changing from a more or less static and preformistic conception to a dynamic and epigenetic one. The formal correlation of individual genes mapped to specific loci on the chromosomes with certain characters has only a limited meaning. . . . One trait appears to have a simple correlation to one gene only as long as the other genes of the same action chain and of other action chains which are part of the same node, remain the same. (Rheinberger and Müller-Wille 2004, quoting Kühn, 1941, 258)

[4] Sturtevant's (1932) utilizing specific genes as markers in the study of organ differentiation during embryogenesis in *Drosophila* was a significant exception.

[5] It is instructive to juxtapose present-day genocentric considerations with those of the old notions of pleiotropy, though in the *reverse* direction, namely the efforts to identify *the DNA-sequence* which may be authoritatively defined as *a gene*. Should the multiple alternative messenger-RNAs extracted from a given DNA-sequence be all considered the products of one gene, or may a DNA-sequence embrace multiple, partly overlapping genes?

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Genetics: The Taming of Darwinism

Whereas heredity and development could arguably be viewed as separate or identical disciplines, depending on whether the emphasis was on the physiological aspects of developmental changes or on the generation-stability of development, the relation of heredity and evolution was unequivocal as has been laid down by Darwin's "provisional hypothesis of pangenesis" in *The Variation of Plants and Animals Under Domestication* (1868). Bateson adopted Mendel's hypothesis immediately upon reading de Vries' 1900 paper because it was consistent with his notions of evolution by discontinuous steps. Contrary to Bateson's conclusions that relied on the a priori theory of "Mendel's Law of Hybridization," concerning the organization of biological material, Karl Pearson (1857–1936), the student of positivism, argued for a position that was based on statistical observations, ostensibly without prior theoretical assumptions. This, he claimed, was represented in the "Law of Ancestral Heredity" (at least, once the parameters introduced by Galton had been eliminated from it).

However, already in 1902 it was shown by Udny Yule that *mathematically* one notion could be reduced to the other. Sixteen years later R. A. Fisher (1890–1962) too showed that mathematically the Law of Ancestral Inheritance can be reduced to that of Mendelian Inheritance (Fisher 1918). Yule and Fisher, however, had different agendas.

A careful analysis of Yule's comments (Yule 1902; see also Tabery 2004) shows that the dispute between Pearson's biometricians and Bateson's Mendelians was one between an organismic, top-down phenomenological descriptive analysis of the variability of a race (= breeding population) and a bottom-up particulate reductive analytical interpretation of individual (or pure line) character differences in hybridization experiments.

> There has always been a good deal of misunderstanding between biologists . . . due in great part, I believe, to the fact that [they] use such terms as *heredity*, *variation*, *variable*, *variability*, in precisely the same signification. . . . The employment of quantitative methods necessarily leads to the use of such expression in a more precise signification . . . .
>
> Quite generally, the statistician speaks of a character as *inherent* whenever the number or "constant" B [in the equation $Y = A + B.X$] is greater than zero. . . .
>
> The distinction between continuity and discontinuity of variation, between inheritance of attributes and of variables do not seem to me to be of *necessary* importance for the theory of heredity; . . . The real and important distinction seems to lie between the phenomena of *heredity* within the race, and the phenomena of *hybridization* that occurs on crossing two races admittedly distinct. (Yule 1902, 195–199; emphasis in original)

Mendelism is concerned with *hybridizations*. Whereas *Heredity* represents the population-aspect of inheritance, *hybridization* is the method to study the inheritance of specific difference characteristics between individuals. The Law of Ancestral Heredity is

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concerned with *heredity*, it is a law that regards the correlation of variance in one generation of the population with that of another; we would say that it is a law in population genetics. Yule made this most explicit a year later, opening his paper: "The statistical theory of heredity, as developed in the work of Galton and Pearson, concerns itself with aggregates or groups of the population and not with single individuals" (Yule 1903).

The statistician's notion of "ancestral heredity" is: "will a knowledge of the grandparent's character enable one to increase the accuracy of the estimate" of the character of the grandchildren above that obtained from the knowledge of the character of the parent? "If the answer to the question be in the affirmative, . . . then there is what may be termed a *partial* heredity from grandparent as well as from parent" (Yule 1902, 201; emphasis in origianl). The law that may be deduced is "that *the mean character of the offspring can be calculated with the more exactness, the more extensive our knowledge of the corresponding characters of the ancestry*, may be termed the Law of Ancestral Heredity" (Yule 1902, 202; emphasis in original). This is an early version of the breeders' concept of later years of *heritability*, which was formulated in terms of Mendelian genetics as the ratio of genetically caused (additive) variability to total variability of a character in a population (Rieger et al. 1991). Noticeably, Yule pointed out that "It is difficult to suppose that the weight attached to pedigree is based on nothing but illusion" (Yule 1902, 202) – it begs for a hypothesis, and this was provided by Mendel's theory of hybridizations.

Fisher is generally regarded as "the first to successfully put forth a theory of the relationship between biometry, Darwinian evolution, and Mendelian inheritance," and his paper "is considered to be a direct descendent of Yule's earlier suggestion" (Tabery 2004, 82). However, contrary to Yule's perspective of the demographic fact of the inherited variation in the population for which Mendelism may or may not provide a good theoretical explanation, Fisher was an ardent Mendelian reductionist who endeavored to explain inherited variance of populations from his genocentric perspective. As put by Tabery, "For Fisher the ancestral law was a special case of the Mendelian principle. For Yule, the Mendelian principles were a special case of the ancestral law" (ibid., 90–91). Fisher claimed that "if one *first* supposes Mendelian inheritance, *then* one can derive the correlation between relatives, resulting in the ancestral law of heredity" (ibid., 83; emphasis in original). In other words, Fisher provided a *conceptual reduction* of biometry's law of ancestral heredity: He took the Mendelian principles of inheritance as the explanatory base and then derived the biometric law of ancestral heredity to show that the statistical law was just a special case of the physiological law (Sarkar 1998, 106). Fisher was aware that he came upon "the Law of Ancestral Heredity as a necessary consequence of the factorial mode of inheritance" (ibid., 83, quoting Fisher 1918, 421). In the era when particulate gene-centered reduction gained primacy, Mendelian explanation made the Law of Ancestral Heredity redundant. Thus Fisher laid the foundation for the Modern Synthesis of Huxley and colleagues two decades later, which turned the theory of evolution into a theory of gene frequencies or population genetics.

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But Yule, by juxtaposing Pearson's support for the Ancestral Heredity Theory and Bateson's claim for the Mendelian theory, also laid bare important aspects of the role that reductionist heuristics play in how scientific deductions are carried out.

> The fact that although the theory of ancestral contribution to heritage implies the law of ancestral heredity, the converse is not true: the law of ancestral heredity need not in any way imply actual physical contributions of the ancestry to the offspring. The ancestry of an individual may serve as guides to the most probable character of his offspring simply because they serve as indices to the character of the germplasm as distinct from his somatic characters. (Yule 1902, 206)

Mendel's Laws and their relation to the Law of Ancestral Heredity, "cannot at least be 'absolutely inconsistent' with each other, as Mr. Bateson contends." The Law of Ancestral Heredity is certainly a deductive law of nature of wide generality which cannot be dismissed. Mendel's inductive Laws, Yule assumed to be true also. "The problem is to delimit their respective spheres, and shew in what way the one type of law may pass into the other, or the two even coexist" (Yule 1902, 207). Whereas Pearson and Galton deduce from ancestral generations, presumably with no hypothesis implied, Mendel's laws, *ex hypothesis* induce forward, to future generations (Gayon 2000). Starting with Galton-Pearson's descriptive law:

> The value of the work of Mendel and his successors lies not in discovering a phenomenon inconsistent with that law [of Ancestral Heredity], but in shewing that a process, consistent with it, though neither suggested nor postulated by it, might actually occur. (Yule 1902, 227)

Mendel in Retrospective: Genocentricity and Its Discontents

Mendel's impact on the evolution of the science of heredity, from the foundations laid down in the 1860s and the establishment of the science of genetics in the 1900s through its shifting relationships with the disciplines of development and of evolution during the twentieth century, and its triumphs as systems' analyses entering the twenty-first century, behooves another examination of the mutual roles of hypotheses and of observations and findings that engendered this science.

Although not intended by Mendel's hypothesis, conceptual reductionism or genocentricity became the dominant driving force in genetic thought throughout most of the twentieth century. It must, however, be kept in mind that the origins of genocentricity or more accurately those of hereditary-determinism, can be traced to the late nineteenth century. With the intensification of the interrelationship of science and society, and the appearance of the scientists as professionals in their own right, biological determinism became a weapon, as well as a shield, of the growing

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community of scientists who considered it their duty to emphasize the social relevance of their science, yet had to face their inability to provide unequivocal answers.

Eugenics is, of course, the first that comes to mind. But also Galton's Law of Ancestral Heredity, much like Darwin's pangenesis, was an ad hoc hypothesis, in which environmental effects had to be explained away. Ruth Schwartz Cowan noted that of all things that Galton wrote in *Heredity Talent and Character* in 1865, "he ended his argument against the inheritance of acquired characteristics with a rough statement of the continuity of germ plasm, the principle that we usually associate with the name of August Weismann and with the year 1883, . . .[as] the result of *sociopolitical rather than biological imperatives*" (Schwartz Cowan 1977, 142; my emphasis). A few years later Galton created a physiological theory of heredity, the stirp theory that embodied the principle of continuity of germ plasm. "The idea of continuity of germ plasm was absolutely essential for Galton's scheme" of human breeding if it had to compete with that of indoctrination or education in averting the social problems of his time (ibid., 143). More recently, John Waller pointed out that "Heredity came to imply relative fixity and resistance to therapeutic intervention. Moreover, the concept often provided physicians and alienists with a useful rationalization when therapeutics proved impotent" (Waller 2001, 461). He quoted a poem of John Byrom, probably written in the 1730s, but published in 1894, that beautifully exposed the inclination of scientists to explain-away phenomena by hereditary determinism, which was formulated by providing names:

> When our distempers did their name receive,
> (One instance more, good doctors, by your leave),
> Some chronic matters, such as gout and stone,
> That would the fare of no *arcana* own,
> To save their Credit these, the learned dons,
> Cried out, were fix'd hereditary ones:
> If a man's father, grand- or great-grand sire;
> Had the same, 'twas needles to enquire;
> Plain was the case, and safe the doctor's fame;
> The poor old ancestors bore all the blame.

Whichever way we take this, no wonder that the differentiation of phenotype and genotype, as introduced by Johannsen in the 1910s, was superposed on the Weismannian theory of segregation of the germ-line from the soma. Thus, it became crucial in making "transmission genetics" a study of heredity, presumably independent of embryology and development. But not less significant a consequence of the reductionist, bottom-up drifting apart of *Entwickelungsmechanik* and genetics was the "ugly fact" that "evolutionary biologists have only rarely been able to make specific predictions regarding the patterns studied by the reductionist research tradition." As Leo Buss noted in his *The Evolution of Individuality,* the "remarkable awakening of interest and change of opinion" among working embryologists with respect to evolution came

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only when "molecular biology has suddenly become a comparative and inevitably evolutionary discipline. A new 'fossil record,' writ in the genome, is now accessible and being read in a necessary piecemeal fashion" (Buss 1987, vii).

Initially, with the presentation of the structural organization of DNA in 1953, the notion of genetic reductionism, and inadvertently also that of genetic determinism, got a strong boost. As Watson and Crick (1953) pointed out at the conclusion of their first paper, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material," both for replication and for catalyzing specific gene products. Notwithstanding, molecular biology, the triumph of genetic reductionist determinism, already carried the seeds of discontent.

The detailed power of the molecular analysis challenged the old concepts by confronting them to the utmost. As late as 1995 Harvey Lodish, a leading cell biologist, still foresaw that "predictions of protein structure and function will be accurate enough so that one can deduce, automatically, the relevant properties of many important proteins, as well as the regulation of their expression . . . from the sequence of genomic DNA alone" (Lodish 1995, 1609). Many human and other organisms' traits that follow Mendelian patterns of inheritance have been labeled "genetic," and many of the genes involved have been mapped, their mutations identified, and screening programs for them instituted. Such a "geneticization," or the tendency to reduce trait differences to genetic ones is expressed in the increasingly popular notion of "the gene for" (Gannett 1999; see also Nelkin and Lindee 1995). Whereas this reflects the extreme deterministic image that genetics acquired, a growing awareness of the more complex traits, ones for which environmental contributions are known to be significant and their genetic component could not be attributed to a single gene, emphasized the urgent need for theoretical and empirical methods that would allow a systems approach. As it turned out, toward the end of the century, the ambitious technical project of mapping the complete human genome, which had raised many eyebrows among theoretical scientists and philosophers, generated – out of necessity – new tools, empirical as well as theoretical, to meet the challenge. Consequently, we entered the twenty-first century to a large extent with a challenge similar to that of the beginning of the previous century, but this time we are much better equipped to face its intricacies both empirically and theoretically.

Comparing the wording of a recent statement by Francis S. Collins, head of the National Human Genome Research Institute at a workshop on *Human Genome Variation and 'Race'* at Howard University, on May 15, 2003, with one of ninety years earlier, which expresses exactly the same notion, by the eugenics-determinist Charles B. Davenport, makes the change of contexts amply clear:

> In many instances, the causes of health disparities will have little to do with genetics, but rather derive from differences in culture, diet, socioeconomic status, access to health care, education, environmental exposure, social marginalization, discrimination, stress

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> and other factors. Yet it would be incorrect to say that genetics never has a role in health disparities. . . .
>
> The question of whether genetics will explain a substantial proportion of health disparities . . . is largely unanswered . . . (Collins 2004)

And:

> In the study of human heredity it has first of all to be recognized that progress will be made only as traits are studied one at a time. The modern science of heredity, indeed seeks as the element of study the "unit character." What are unit characters can, however, be told only by breeding experiments in which the true units reveal themselves as relatively, if not absolutely, constant, unalterable, indivisible things. . . . The criticism may be made that not all the traits, especially the diseases, given here have any hereditary basis . . . yet it cannot be denied that all have an hereditary basis. Even tuberculosis, syphilis, and the plague are the product of a specific germ acting on a susceptible protoplasm and it is this susceptibility that is the inheritable factor. (Davenport 1912)

However, the problematic relationships between reduction as a methodology and reduction of a conception have been highlighted by Roux already a century ago: When he endeavored to turn embryology into a bottom-up research project, he emphasized the need for simple methodologies, and at the same time, the caution that must be exerted in interpreting the data as simple concepts:

> Among biologists there is a tendency derived from inorganic sciences, *to regard the hypothetical deductions which appear to us to be the "simplest" as having the greatest probability for the very reason that they seem so simple*. [But a]lthough much has been done on this assumption, and unfortunately must be done, . . . nevertheless this method must always be applied with great reserve to normal biological phenomena, . . .
>
> Thus we suppose that we are really simplifying matters when, e.g., we attribute in consequence of functional adaptation many typical and purposive forms to the self-constructive effects of use. The correctness of this *principle* and its application in many cases has long been capable of direct proof. Nevertheless, we observe that many structures which might be the result of this principle, . . . are already established before there is an opportunity for them to exercise their definite functions. (Roux [1894] 1986, 119; emphasis in original)

Only "forward deductions" from experiments that control the causal force, can be "certain." There is no sense (at least in living systems) in isolating one causal force, independently of other causes, but this was the only way that a cause could be studied directly. Roux would have been happy if it were possible "to reproduce *synthetically* in an inorganic way *structures, forms, and processes which resemble as closely as possible*, those of the organic world." But as he noted, "even in cases where it is claimed that such a reduction has been brought about, it appears that the part which the simple components contribute to the formation in question, as compared with that of the coöperant

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complex components, has been considerably overestimated" (ibid., 128–129; emphasis in original). Embryologists, in view of such a program as Roux's, were caught between holistic concepts of organisms as complex systems that cannot be simplified and studied effectively by the methods of physicists and chemists, and the reductionist need to apply experimental mechanics in order to study "real" causes. Geneticists by having been offered distinct and discrete entities, the genes, believed that they could successfully apply not only methodological, but also conceptual reductionism. Since then we have advanced in our molecular and computational technologies, and the old dream may again appear luring to the modern genetic engineer. Yet, the same problem may exist in today's studies in genomics which try to follow simultaneously many *individual* causes. Unless a conceptual change takes place, the risk remains that the methodologically isolated forces would be inadvertently identified with the conceptually assumed forces.

The challenge, as I see it, is to sort out the reductionist methods of empirical research – which have been and will be irreplaceable in research in the life-sciences in general, and in genetic research in particular – from those notions of conceptual reductionism that may have had tactical or hypothetical value, but must be replaced by systems' conception, which are, after all, that unique specificity of life on earth. James Griesemer's (2000) suggestion that we should think of both development and inheritance as processes reducible to reproduction may be a step in the direction of maintaining methodological reduction as an efficient research instrument within the conceptual framework of organisms as integrated systems.

If we return for a moment to the 1930s and 1940s when Niels Bohr and Erwin Schrödinger wondered "What is Life," and physicists, in the footsteps of Max Delbrück, flocked into biological research to discover the specific Laws of Nature hidden in living creatures, we may say now, with some confidence: There are no special laws of the living world, neither *Lebenskraft*, nor *Entelechy*, nor any need for an Anthropomorphic Principle or divine power. It is just the evolution of the material world, as put forward by Darwin, and probably contrary to that believed by Mendel.

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