

century: the ‘gemmules’ of Darwin, ‘physiological units’ of Herbert Spencer, ‘pangenes’ of de Vries and ‘bioblasts’ of Richard Altmann had been widely considered. The most elaborate 19th century theory of heredity and development was that of August Weismann who postulated the existence of a hierarchy of determinants, organized in chromosomes, which would segregate out of the cell nucleus in the course of development and determine cell types. Weismann’s theory was refuted in the 1890s when experimental embryologists showed that the fate of a cell during ontogeny was regulated at least in part through its relations with others.

Johannsen’s aim in introducing the term ‘gene’ was to dissociate Mendelian genetics from all such discredited, speculative conceptions of self-reproducing vital entities. ‘Of all the Weismannian army of notions and categories’, he said, ‘Mendelism may use nothing’.¹ The nature of the gene was of course not known, but the idea that the Mendelian factors were ‘discrete particles of the chromosomes’ was not a corollary of his genotype conception.¹ Johannsen’s ‘gene’ did not have the power to reproduce itself, to grow and to assimilate; it did not possess an independent life of its own. ‘The gene’, he said, ‘Was nothing

but a very applicable little word’.¹ As he later put it, ‘The Mendelian units as such, taken *per se* are powerless’.⁵

Indeed, it behoves us to take note that Johannsen’s genotype conception of heredity is a version distinct from two erroneous views, which are heard too often to this day, that ‘genotype determines phenotype’ and that the ‘gene’/DNA is self replicating.

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Commentary: A century of Mendelism: on Johannsen’s genotype conception

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Inundated by so many recent exciting developments in genomics, we missed the 100-years anniversary of the re-introduction of Mendelism and especially the foundation of the genotype concept following the publication of the paper that changed the face of modern genetics, namely Johannsen’s 1911 ‘The genotype conception of heredity’.¹

Wilhelm Johannsen (1857–1927), a pharmacologist by training, served, without any formal university degree, as assistant in the Chemical Department of the newly founded Carlsberg Laboratorium in Copenhagen. In 1892 he was appointed lecturer and later professor of plant physiology at the Royal Veterinary and Agricultural College of

Copenhagen. Finally, in 1905 Johannsen was appointed Professor Ordinarius in plant physiology at the University of Copenhagen, and in 1917 he became rector of the university.²

The notes of the class in heredity which Johannsen taught, first published in 1905 in Danish, were extended in 1909 into a German volume of 25 lectures regarding the *Elements of the Exact Theory of Inheritance* (Elemente der exakten Erblchkeitslehre).³ Updated second and third versions were published in 1913 and in 1926, respectively. Already in the first edition, Johannsen rebelled against the notions of heredity of early Mendelian colleagues,

although he maintained the style of a diehard more than that of a rebel.⁴ Johannsen's contribution to genetic thinking was recognized and he was invited to address the symposium on 'The genotype hypothesis' at the 1910 Christmas Meeting of the American Society of Naturalists in Ithaca, New York, but was unable to attend. However, he published his long paper in the *American Naturalist*¹ of 1911, in which he expounded his genotype conception of heredity. Although he eventually diverted too much into secondary details, the theory must be recognized as a creation that provided the theoretical foundations or the framework for the upcoming reductionist material science of genetics, quite beyond the perception of its instigator. Its author travelled to America a year later.

Most of Johannsen's publications are in Danish and German. Besides the 1911 paper, I am acquainted with only one other English paper by him, of 1923, 'Some remarks about units in heredity', published in the Scandinavian geneticists' journal *Hereditas*,⁵ as a kind of afterthought of the 1911 paper.

The first decade after the 'rediscovery' of Mendel's work in 1900 was devoted mainly to investigating the extent of his rules of segregation and the modifications needed to make the rules of Mendelian segregation universal. But questions on the theoretical context of the biological meaning of such rules had already been brought up. Pivotal was the establishment of the genotype conception—as initially introduced by Galton and by Weismann—versus the old transmission conception of heredity. According to Galton's 'stirp' and Weismann's 'Keimplasma' notions, the elements responsible for inheritance directly involved the different specific organs or tissue groups of the individual developing from the zygote in question. Johannsen opposed such preformationist notions. He also opposed Weismann's chromosomal theory, which suggested 'that discrete particles of the chromosomes are "bearers" of special organizing functions in the mechanism of ontogenesis, a chromatin representative of an organ or a group of tissue'.

Johannsen was very explicit:

These two ideas: that 'elements' in the zygote correspond to *special organs*, and that *discrete particles of the chromosomes* are 'bearers' of special parts of the whole inheritance in question are neither corollaries of, nor premises for, the stirp- or genotype-conception. Those special ideas may have some interest as expressions of the searching mind, but they have no support in experience; the first of them is evidently erroneous, the second

a purely speculative morphological view of heredity without any suggestive value.

Thus Johannsen denied that:

- i. 'Elements' in the zygote correspond to special organs.
- ii. Discrete particles of the chromosomes are 'bearers' of special parts of the whole inheritance in question.

He took from Galton and Weismann the notion of the genotype or, as he called it, 'the genotype conception' but denied the two-way correspondence of organ to genes and genes to organs.

The 'gene' is nothing but a very applicable little word...it may be useful as an expression for the 'unit factors', 'elements' or 'allelomorphs' in the gametes, demonstrated by modern Mendelian researches...As to the nature of the 'genes' it is as yet of no value to propose any hypothesis; but that the notion 'gene' covers a reality is evident from Mendelism...[A] quite natural reaction against the morphologico-phantastical speculations of the Weismann school – it may be emphatically recommended to use the adjectival term 'genotypical' instead of the noun 'genotype.' We do not know a 'genotype' but we are able to demonstrate 'genotypical' differences or accordances.

Johannsen turned to the German term *Reaktionsnorm*, used by Woltereck, for the sum total of the potentialities of the zygotes, as nearly synonymous with 'genotype'. 'That these potentialities are partly separable ('segregating' after hybridization) is adequately expressed by the 'genotype' as composed of 'genes'.

In the era of prospering post-Darwinian determinist life-sciences, it was in the Carlsberg Laboratories that Johannsen became interested in the nature of variability in plants.

All 'types' of organisms, distinguishable by direct inspection or only by finer methods of measuring or description, may be characterized as '*phenotypes*'. Certainly phenotypes are *real things*; the appearing (not only apparent) 'types' or 'sorts' of organisms are again and again the objects of scientific research.

Since most researchers of heredity until that time chose to work with unequivocal qualitative type-differences there was no problem of conceiving relevant, genotype differences as distinct observed phenotype properties. Once Johannsen's interest centred on the exact aspects of a science of heredity of quantitative variation, he turned to self-fertilized plants, especially barley and beans, to minimize initial hereditary variability among progeny of given individuals. Assuming that the remaining variability among the progeny of given individuals was 'environmental' (and

controllable) with respect to the properties studied, his attention centred on a rational statistical analysis of genotypic variation, as deduced from observed phenotypic variability.

In 1900 Johannsen started a series of breeding experiments with a bag of bean seeds that he purchased. Soon he established that several generations of selfing produced lines each with its specific mean about which variance was reduced compared with that of the mixed purchased sample, but not eliminated. For the properties he followed (seed weight and the ratio of seed breadth to width that Johannsen measured) in progeny of the original commercial sample of beans, partial regression to the mean of the parental population was observed, whereas full regression to the mean of the line was detected in the progeny of individual beans after several generations of selfing. In 1903 Johannsen created the expression 'pure line', and formulated a new interpretation of Galton's law of regression: regression to the mean is total in pure lines; partial regression indicates mixture of pure lines. Johannsen reached the enormously important conclusion that no heritable variation remained in pure lines, or as he formulated it, 'the conviction that *selection is not able to shift the nature of genotype*'.

Johannsen soon realized that Darwinian thinking had put the emphasis on the transmission of properties from ancestors to their descendents rather than on the mechanics behind the transmission of these properties. Such a 'transmission conception' of heredity appears to be inevitable for, say, the palaeontologist, who has only post-factum fossil evidence of the processes of inheritance and natural selection at his disposal. Not so for the experimental biologist who may ask for the rules of inheritance of inter-organismic (phenotypic) variability that serves as the raw material for the evolution by differential (genotypic) transmission from parents to offspring. Johannsen, like Mendel before him, understood that since the observed variability may be due to different factors, before carrying out experiments on the inheritance of specific heterogeneous factors one should control the sources of their variability. Mendel inbred the pea seeds that he purchased for 2 years before he chose seven properties appropriately conspicuous and stable on the available level of variation for his hybridization experiments and for the (almost) unequivocal classification of the progeny.⁶ Johannsen inbred his bean plants for several generations until pure lines were obtained, namely until the mean of the properties followed in each line was constant from one generation to the next. Thus, effects of hybridization between pure lines could be assigned to differential factors of heredity. This was Johannsen's 'genotype conception'.

So far Johannsen adopted the analytical reductive methodology of the sciences. But interestingly, Johannsen was not impressed by the imperialism of the physics-style conceptual reductionism that prevailed in biological research of the first half of the 20th century. He rejected the attempts of his forerunners, primarily Galton and Weismann, who suggested preformationist versions of theories of inheritance, such as Galton's stirp hypothesis that suggested the transmission of specific anlagen of different tissues or organs, or Weismann's germ-plasm theory that conceived of the nucleoplasm as the carrier of the elements of inheritance:

Galton, in his admirable little paper of 1875, and Weismann, in his long series of fascinating but dialectic publications, have suggested that the elements responsible for inheritance (the elements of Galton's 'stirp' or of Weismann's 'Keimplasma') involve the *different* organs or tissue-groups of the individual developing from the zygote in question. And Weismann has furthermore built up an elaborate hypothesis of heredity, suggesting that discrete particles of the chromosomes are 'bearers' of special organizing functions in the mechanism of ontogenesis, a chromatin-particle in the nucleus of a gamete being in some way the representative of an organ or a group of tissues.

Johannsen rejected the conception of heredity as transmission of traits. His interest in the physiology and embryology of inheritance took him to adopt an organismic, holist position: His notion was actually an extremely modern systems approach, of adopting a strict reductionist *methodology* to analyse advanced *conceptual* interacting entities. No autonomous particles for that property or another, and no specific elements of inheritance in the nucleus, rather the whole organism's biology and its cells' interactions with neighbouring cells, produce the embryo and the organism that emerges. There are no specific cellular elements, neither nuclear nor chromosomal, involved in heredity.

These two ideas: that 'elements' in the zygote correspond to *special organs*, and that *discrete particles of the chromosomes* are 'bearers' of special parts of the whole inheritance in question are neither corollaries of, nor premises for, the stirp- or genotype-conception.

Johannsen would have been stunned if he heard present day free use of 'gene' or 'genetic' (as well as DNA) as applied to any property or behavior which is claimed to be common to any association of (human or non-human) individuals.

Johannsen—as noted—was genuinely interested in the evolution of the plant's quantitative varying properties. According to Galton's rule of ancestral inheritance, the mean of the progeny of selected parents regressed upon inbreeding toward the mean of the population, rather than

corresponding to that of the selected parents. This appeared to expose the nature of the population's variance, as allowing smooth continuous transition by selecting of one species towards another. Johannsen, however, rejected the Darwinian conception of the evolution of species as continuously changing entities and resigned to the evolution of stable species by letting the elementary species change discontinuously by mutations. He also vehemently rejected the Weismann school's 'morphologico-phantastical speculations' and, as noted, although he invented the terms 'genotype' and 'gene', he recommended using the adjectival term 'genotypical', asserting that 'These potentialities are partly separable ("segregating" after hybridization) is adequately expressed by the "genotype" as composed of "genes"'.³

As noted, Johannsen, like Mendel before him, was very much aware of the variance of properties. However, whereas Mendel worked with a model of inheritance that by and large reduced the phenotype to the genotype, Johannsen did not care for the (physical existence of) entities of inheritance but rather for the properties of the traits: 'We do not know a "genotype", but we are able to demonstrate "genotypical" differences'.

Perhaps the most profound aspect of Johannsen's insight was the physiological and embryological one. Johannsen's segregation of genotype and phenotype made the distinction between preformationists and epigenesists irrelevant. Heredity could now be conceived as a process, a production: it was competent to investigate the causes of development and function, rather than merely those of transmission of factors that unfold to become traits.⁴

Genetics of today is hardly engaged in hereditary transmission but rather in the physiology and embryology of turning DNA-coded information into properties.

Significant is Johannsen's repeated reference to Woltereck, who studied the changes in the morphology of *Daphnia* populations sampled in different lakes when grown under defined laboratory conditions (such as temperature or nutrition).⁷ As Johannsen noted (below), Woltereck's German term *Reaktionsnorm* is nearly synonymous with 'genotype' in so far as it is 'the sum total of the potentialities of the zygotes in question'.

That these potentialities are partly separable ('segregating' after hybridization) is adequately expressed by the 'genotype' as composed of 'genes'. The 'Reaktionsnorm' emphasizes the diversity and still the unity in the behavior of the individual organism...[nevertheless] the *personal qualities* of any individual organism do not at all cause the qualities of the offspring; but the qualities of both ancestor and descendant are in quite the same manner deter-

mined by the nature of the 'sexual substance'—i.e., the gametes—from which they have developed.

Acquainted with statistical methods, once Johannsen extracted various pure lines from a collection of wild-types, he could claim that 'Galtonian law of regression and its corollaries elaborated by Pearson pretended to have established the laws of "ancestral influences" in mathematical terms' were an artefact. They were nothing but 'interesting products of mathematical genius...but they have nothing at all to do with genetics or general biology!...In pure lines no influence of the special ancestry can be traced'. One cannot over-estimate the impact of Johannsen's statement:

An ancestral influence in heredity is, plainly speaking, a term of the 'transmission-conception' and nothing else. The characters of ancestors as well as of descendants are both in quite the same manner reactions of the genotypical constitution of the gametes in question.

Johannsen implanted genetics directly in the heart of reductionist science:

The genotypic constitution of a gamete or a zygote may be parallelized with a complicated chemico-physical structure. This reacts exclusively *in consequence of its realized state*...The genotype-conception is thus an 'ahistoric' view of the reactions of living being—of course only as far as true heredity is concerned.

One should note this last caveat—Johannsen was obviously aware not only of the 'evolution of human civilization [where] we meet with *true ancestral influence*' but also of possible impacts of the phenomenon of life being a historic sequence.⁸ And as Johannsen noted in spite of his reductionist, bottom-up operationalism:

The very 'radical' form of the genotype-conception advocated here may be too 'theoretical' to be carried through in all its consequences in cases of practical experiments in genetics....As to the analogy with the genotype we touch here the question whether the genotypical constitution of gametes may not be accompanied by some ancestral or accidental 'impurities' from the individual organism in which the gamete was developed.

Still, he makes the point that 'the principle of pure lines or, generally, pure culture' contributed also to such problems as 'the celebrated question of the inheritance of "acquired characters"'. Evidence indicates that 'changes of the genotypical constitution are produced by steps, discontinuously'. Mutations, in modern language notwithstanding, 'as yet no experiment with genotypically homogeneous cultures has given any evidence for the Lamarckian view, the most extreme "transmission"-conception ever issued.

Thus, the notions of pure lines and the discontinuity between different genotypes that it advocates, which have

been energetically contested by biologists who believe in continuous evolution, has far-reaching consequences on the perception of life. Take Woltereck for example, who confessed openly his belief in continuous evolution, who ‘remarks that for a convinced selectionist of the Weismann school the new genotype conception is a “hard blow”’. Johannsen pointed out the importance of his distinction:

Of course the *phenotypes* of the special characters, i.e. the *reactions of the genotypical constituents*, may under different conditions exhibit all possible forms of transition or transgression—this has nothing at all to do with constancy or inconstancy of genotypical differences...The essential point in the whole matter is, of course, that a special genotypical constitution always reacts in the same manner under identical conditions—as all chemical and physical structures must do.

Once the ‘discontinuity and constant differences between the “genes” of Mendelism had been established, Johannsen pointed at the large-scale experiments of Bateson and many others who verified ‘the inadequacy of the personal quality of heredity’.

At the same time it overthrows totally the idea of ‘*organs*’ as being represented by the unities of the ‘*stirp*’, pointing out that the personal qualities of *the organism in toto* are the results of the reactions of the genotypical constitution. The segregation of one sort of ‘gene’ may have influence upon the whole organization. Hence the talk of ‘genes for any particular character’ ought to be omitted, even in cases where no danger of confusion seems to exist.

Johannsen is correct that it ‘should always be borne in mind that the Mendelian analysis is *purely relative*’. He mentioned the well known facts, that a ‘character’ may be dominant in some hybrids but recessive in others, and that segregation in different cases may be different, indicating that ‘characters’ are complicated reactions. Therefore the ‘units’ or ‘unit-factors’ stated in Mendelian work are consequently quite provisory, depending essentially upon *the number of genodifferences* in the special crossing’.

In such a context one has also to examine Johannsen’s disfavour of the chromosomal theory of inheritance as developed by Morgan and his students. Only later, with overwhelmingly accumulated evidence in its favour, did Johannsen accept in his 1923 paper the chromosomal theory of inheritance. For Johannsen, the question of chromosomes as the presumed ‘bearers of hereditary qualities’ seemed to be an idle one:

I am not able to see any reason for localizing ‘the factors of heredity’ (i. e. the genotypical constitution) in the nuclei. The organism is in its totality penetrated and stamped by its genotype-constitution. All living parts of

the individual are potentially equivalent as to genotype-constitution.

Like Johannsen also the early T. H. Morgan felt a ‘distinct disinclination to reduce the problem of development to the action of specific particles in the chromosome’, at least in the sense of the Roux-Weismann assumption which argued for ‘nicely separating at each division the different kinds of materials of which the chromosomes are composed’.⁹ Both Johannsen and Morgan preferred the top-down approach of organismal development to the strict bottom-up conception of the Mendelian factors:

Those not engaged in the immediate work itself have, I believe, often been misled in regard to the meaning attached to the term factor, and by the assumed relation between a factor and a unit character. The confusion is due to a tendency...to speak of a unit character as the product of a particular unit factor acting alone.¹⁰

Morgan ascribed this to ‘the attempt to impute to the factorial hypothesis the same interpretation that Weismann made use of in his theory of determinants’.¹⁰ But the more the experimental work in Morgan’s laboratory advanced, the more the chromosomal theory of inheritance with discrete genes linearly arranged along them advanced, and eventually even Johannsen had to acknowledge it. Beadle and Tatum’s^{11,12} notion of ‘one gene—one enzyme’ further reduced the notion of inheritance being the transmission of structural and functional information and was soon extended to the molecular level: the nucleotide sequences of the DNA being nothing but coded information for embryo’s development and function. Genetics was becoming less directed as a theory of transmission, and more as the theory of unfolding of developmental structures and functions, given the transmitted coded information that turned out to be an integrated system of structure and function in which the reducible details play their role as parts of the system.

Heredity may then be defined as *the presence of identical genes in ancestors and descendants*, or, as Morgan says in full accordance with this definition: ‘The word heredity stands for those properties of the germ-cells that find their expression in the developing and developed organism’.

Johannsen’s contribution of the genotype conception remains that of making geneticists alert to the insufficiency of reductive science inherited from the physico-chemical disciplines. He directed us back to the study of life as a historical incidence and of the selection of self-sustaining interactive systems that happened to occur. When we consider that living beings are complex interacting systems, it is

no wonder that only 1% to 2% of the genome is allocated to genes that code for proteinaceous products. Building the system and maintaining it demands much more.

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Commentary: Wilhelm Johannsen and the problem of heredity at the turn of the 19th century

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Darwin's theory of the origin of species by means of natural selection was essentially dependent on his views about inheritance. The character had to be inherited, to some extent at least, if the mechanism of natural selection was to produce evolutionary changes. Only hereditary variability would work. But Darwin's theory of heredity was primitive. As the Danish plant physiologist Wilhelm Johannsen wrote, Darwin's theory of pangenesis was more or less the same as that which Hippocrates had held 22 centuries earlier [p. 54].¹ With the cytological discoveries of the late 19th century, and the efforts to give plant and animal breeding a scientific basis, a new era began. Botanists and plant breeders in particular played a central role in the decades around 1900, when the founding of genetics took place.

The chromosome theory as outlined by Thomas Hunt Morgan and his co-workers in *The Mechanism of Mendelian Heredity*² was a major benchmark in the early history of genetics. It can be seen as setting the course that

led to the discovery of DNA structure and the beginnings of molecular genetics four decades later. It is worth asking if similar status should be given to Johannsen's 1910 lecture on 'The genotype conception of heredity'.³ This lecture summed up his experimental and theoretical achievements, including a sharp analysis of the concepts of 'genotype' and 'gene'. He had himself coined these terms two years earlier in his magisterial textbook *Elemente der Exakten Erblchkeitslehre* (*Elements of an Exact Theory of Heredity*).⁴

Genotype is the basic concept in Johannsen's 1910 lecture. The stability of the genotype is what makes a science of heredity possible. The concept of 'gene' is derivative. It represents an experimentally identifiable difference between genotypes. From this holistic perspective he developed his criticism of the particulate gene concept that became the basis of mid-20th century Neo-Darwinism, the 'New Synthesis' of genetics and evolution. Johannsen in his later writings praised highly the discoveries of *Drosophila*