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.

Conflict of interest: None declared.

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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 Erblichkeitslehre* (*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 genetics as fundamental novelties[5] (consecutive editions were extensively reworked and thus demonstrate both the continuity and the change in Johannsen's genotype theory), but still insisted that there was more to heredity and to the explanation of evolution than could be explained by such particulate genes.[6,7]

The inheritance of variation

Variation was a central topic in late 19th and early 20th century biology. There were clearly different kinds of variation. But how more precisely to categorize them? What were their causes? And to what extent were they inherited?

In 1896, in a small, popular book *Om Arvelighed og Variation* (*On Heredity and Variation*), Johannsen sketched his programme for a new experimental science of heredity. This science was to be the basis for more adequate explanations of the evolution of species: 'Evolution needs a science of heredity, but not vice versa' [p. 12].[8] The traditional Linnean species were broad classes that often included many subspecies and varieties. Like many contemporary biologists, Johannsen had an interest in the origin of the most limited classes, often called 'elementary species'. This was a question where evolution of species overlapped with plant breeding and was thus accessible to experimental method.

In this book, Johannsen took Francis Galton's biometric methods and theories about heredity and selection as his starting point. Galton's law of regression (also called the law of ancestral heredity)—that the properties of the offspring tend to be more 'mediocre', i.e. closer to the mean of the population, than their parents—was extensively presented and discussed. Johannsen also pointed to Louis Vilmorin's pre-Darwinian studies of heredity by pedigree breeding as a promising method. But August Weismann's lofty speculations on the cytological basis of heredity, embryology and evolution were subjected to Johannsen's subtly ironical criticism.

The fourth edition of Eugenius Warming's textbook *Den Almindelige Botanik* (General Botany) was published in 1901 with Johannsen as co-author. Warming is recognized as one of the founders of modern ecology. Their co-authored textbook of 1901 contained an up-to-date presentation of cytology and fertilization written by Johannsen. He was also responsible for the final chapter on variability, heredity and descent, including 4 pages on Mendelian segregation. Johannsen was well abreast of contemporary discussions about heredity and its cytological basis.

Johannsen listed and discussed five types of variation: (i) polymorphy of species (subspecies, varieties); (ii) variation in hybrids; (iii) 'individual or fluctuating' variations; (iv) conspicuous modifications due to environment; and (v) 'so-called mutations'. The difference between categories (iii) and (iv) and the extent to which variations of category (iii) were inherited were central questions [p. 667].[9]

As the book was finished in the spring of 1901, Johannsen was also preparing his classical bean selection experiment. Inspired by the ongoing debate between Hugo de Vries and the British biometricians, Frank Raphael Weldon and Karl Pearson, he wanted to test Galton's law of ancestral heredity. With the assumption that heredity varied continuously both in time and amount, this law fitted an orthodox Darwinian explanation of evolution as a smooth and continuous process of change. Johannsen sowed a selected set of beans from a batch of the 1900 harvest that he had bought on the market. He processed their offspring in accordance with the pedigree method of Vilmorin. The seed of each plant was separately weighed and measured. This procedure was repeated the next year (1902), keeping track of the offspring from each of the original beans sowed in 1901. Each of them had thus produced a pure line consisting of three generations of individuals that could be subjected to statistical analysis. (In Johannsen's terminology a pure line was defined simply as all descendants from one particular individual.)[10,11]

The trick of Johannsen's experiment was to choose a plant with a very high degree of natural self-fertilization. This meant that hereditary variation due to hybridization had been eliminated through many generations of inbreeding. And by keeping separate the progeny of each individual seed he could also in his analysis eliminate the difference in hereditary type ('elementary species') between the individual seed that started the experiment. In this way he was able to focus sharply on inheritance of type (iii) variation, i.e. the 'individual or fluctuating' variation.

After only two growing seasons emerged a clear result that surprised Johannsen: there was no inheritance of individual variation within his pure lines, they appeared each to belong to one homogeneous hereditary type. This result indicated that only two of the four kinds of variation listed in the 1901 textbook were possible sources for the hereditary variation that natural selection could draw on, namely mutation and hybridization.

The result was quickly published in a 1903 monograph: *Ueber Erblichkeit in Populationen und reinen Linien. Eine Beitrag zur Beleuchtung schwebender Selektionsfragen* (*On Heredity in Populations and Pure Lines. A Contribution to the Illumination of Unanswered Questions Concerning Selection*).[12] He claimed to have shown that the law of ancestral heredity was an illusion. Galton's experiment with sweetpeas had used a population consisting of many different hereditary types—sweetpeas are selffertilizers like beans. By dividing his population into subpopulations, consisting of pure lines with distinct pedigrees, Johannsen was able to separate the hereditary types. He could now show how the regression toward the mean, that Galton had observed for the whole population, simply represented a shift in the frequency of the different hereditary types within the whole population. There was no regression within each of the pure lines.

Nevertheless, Johannsen saw Galton as his main predecessor in creating an exact science of heredity. The 1903 monograph was solemnly dedicated to 'the highly deserving creator of the exact theory of heredity Francis Galton F.R.S. in gratitude by the author'. But the leading biometricians, Weldon and Pearson, did not appreciate Johannsen's discovery, and they probably read the dedication as an insult rather than true gratitude. Pearson and Weldon curtly dismissed Johannsen's conclusion as due to incompetence in statistics. In fact, they claimed, his experimental facts fitted their theory. A fellow British biometrician, George Udny Yule, argued that they had misunderstood Johannsen's concept of biological type, and that his statistics, though primitive, were adequate for the purpose. Johannsen's results were highly important, said Yule, though he doubted the constancy of type would last over many generations. Pearson replied furiously to this defence of Johannsen.[13]

The genotype theory

During the following years Johannsen developed his ideas of biological type into the genotype theory. Soon geneticists with a biometric approach took a keen interest in Johannsen's work in defiance of Pearson. Weldon died in 1906 and did not get much time to reconsider. The terms 'genotype' and 'phenotype' were first introduced in Johannsen's major textbook *Elemente der Exakten Erblichkeitslehere* (1909). This presentation of the genotype theory based on biometric methods established Johannsen as a leading geneticist on the European continent. But it was among the American breeder-geneticists that his ideas were most readily appreciated. In early 1910, American biometricians Raymond Pearl and Charles Davenport were summarily removed from the editorial board of Pearson's journal *Biometrika* as they had started expressing sympathy for Johannsen's genotype idea.[14]

In December 1910 the American Society of Naturalists organized a special symposium on 'The Study of Pure Lines of Genotypes', with a keynote paper from Johannsen. Illness prevented his presence at the symposium. But the following winter, from October to March, he gave numerous seminars and lectures, travelling around the USA. The plant geneticist and breeder George Henry Shull was the general organizer of Johannsen's trip, and cytologist Edmund B Wilson invited him to give a seminar series at Columbia University, home of the Drosophila geneticists.

Johannsen presented his genotype theory as 'the modern view of heredity' [p. 131].[3] He rejected the old 'transmission' view which dated from Hippocrates and had dominated biological thinking until quite recently. This view conceived heredity as a 'transmission of the parent's (or ancestor's) personal qualities to the progeny' [p. 129],[3] according to Johannsen. Darwin's hypothesis of 'pangenesis' as well as the Lamarckian heredity of 'acquired characters' were wedded to the transmission conception. Johannsen also thought that 'the current popular definition of heredity as a certain degree of resemblance between parents and offspring, or, generally speaking, between ancestors and descendants, bears the stamp of the same conception'. No doubt he here had the biometricians' theory of heredity in mind. According to the modern conception, Johannsen explained, 'the qualities of both ancestor and descendant are in quite the same manner determined by the nature of the "sexual substance"—i.e. the gametes—from which they have developed'. It is this common 'sexual substance' which is transmitted and not the '*personal qualities* of any individual organism' [p. 130].[3]

Again and again through his writings, popular as well as academic, Johannsen stressed the fundamental difference between the actual characters of individual organisms and what was transmitted from parents to offspring, between phenotype and genotype as it were. He had a standard illustration, first used in his 1896 pamphlet. The first figure represented Johannsen's own version of Galton's theory of the stirp, each individual is an outgrowth of a continuous stirp. The second represented Johannsen's interpretation of the old view from Hippocrates to Darwin, where the sex cells in each generation are formed under the influence of the personal characters of the parent [pp. 70–71].[1]

```
 A        A        A        A        A
 /        /        /        /        /
_s_______s_______s_______s_______s_____
```

The series of 's'represent the underlying stirp, which continues unchanged from generation to generation. The As are individuals in successive generations. The genotype is identical but the phenotype different.

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__A_____ka_____B______kb____C_____kc____
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The large letters, A, B, C. . .represent individuals in successive generations. The sex cells are presented successively as ka, kb, kc, indicating that they incorporate new hereditary properties for each generation.

Even Galton and Weismann with their ideas of stirp and continuity of germ plasm had not quite succeeded in abandoning the old view, according to Johannsen. But a revision of their ideas through 'the insights won by pure line breeding and Mendelism' had produced the present day 'genotype-conception', which was 'in the least possible degree a speculative conception', he explained [p. 132].[3]

Except for one critical voice, the December 1910 symposium appeared very supportive of Johannsen's theory. J Arthur Harris, biometrician and loyal pupil of Pearson, perceived the symposium as something like 'the country parson's "praise service"', and his job was to introduce a 'note of agnosticism' [p. 346].[15] His polemical paper had a narrow biometric approach and lacked Johannsen's broad biological framework.

Besides Johannsen's selection experiment, Harris' main target was Raymond Pearl's selection experiments on the egg-laying of poultry. Pearl's application of the genotype theory to sexually reproducing animals was an important generalization of Johannsen's idea. The recently excommunicated biometrician stated in his paper that the fatal weakness of the 'statistical' concept of biological inheritance was its neglect of different kinds of variation. The biometric approach assumed that:

> …all variations are of equal hereditary significance and consequently may be treated statistically as a homogeneous mass, provided only that they conform to purely statistical canons of homogeneity [p. 321].[16]

Harris was an associate of Pearson and engaged in large-scale selection experiments on beans, presumably to test the genotype theory. These experiments were carried on for several years, but the results supported Johannsen's genotype theory rather than the biometric view of continuous variation, and they were only published to a limited extent.

The critique of 'Darwinism'

Johannsen was continually concerned with the implications of his views on biological types for evolution. In a popular article of 1903, he pointed out that 'Darwinism' could be a label for quite different theories of evolution. Even Darwin himself had gradually moved 'away from natural selection as the only or main factor in the origin of species and was leaning towards the Lamarckian view, that the conditions of life quite directly can form organisms and thus even without selection produce new forms, new species' [p. 527].[17]

According to Johannsen, four main 'theories' of evolution were 'at the moment on the agenda': (i) direct influence of the environment; (ii) mutations; (iii) selection of continuous variation; and (iv) hybridization. These were not exclusive but could be combined in various ways, like Darwin had combined (i) and (iii). Johannsen argued that his selection experiments strongly supported other evidence against theory (iii), selection of continuous variation. There simply was no good evidence for a continuous supply of hereditary variation in all directions, as orthodox Darwinism, like that of the biometricians, and some forms of neo-Lamarckism, assumed. In his view mutation was the most plausible source of hereditary difference between his pure lines. Mutation was the source of change which natural selection could work on. It appears that Johannsen at this time saw the pure lines in populations of self-fertilizing plants as isolated from each other, and without significant crossing. Thus hybridization was not likely to be important in evolution, and his overall conclusion was that mutation was likely to be the most important source of evolutionary change. He stressed, however, that there were many examples where hybridization in combination with mutation had produced new forms. But this did not mean that hybridization was necessary for evolution [p. 538].[17]

Johannsen's criticism was aimed at 'Darwinism in the narrowest sense', the view that assumed continuous hereditary variation as the basis for natural selection. This included Alfred Russel Wallace and August Weismann as well as the biometricians [pp. 532–33].[17] They had all missed the full significance of the fundamental difference between underlying biological type and the appearance of individual organisms. Johannsen liked to use clear and strong words. In a 1915 survey of the experimental basis of evolutionary theories, for instance, he concluded that Darwin's 'theoretical presuppositions with respect to inheritance were in principle incorrect' and thus 'the Darwinian theory of selection finds absolutely no support in genetics' [p. 659].[18]

Natural selection nevertheless retained an essential role in Johannsen's view of the evolution of species. His point was that it had a purely selective and not a creative role. Only through knowledge of the mechanisms of variation could the direction and the path of evolution be explained. This corresponded well with the later neo-Darwinism of the mid-20thcentury. By changing its ground from continuous variation to mutations, Darwinism could save large parts of its theory of selection, Johannsen explained. The situation was worse for neo-Lamarckism. There was no good evidence for the existence of directed mutations that adapted the organism to its environment [pp. 888 and 898].[19] Johannsen found neo-Lamarckism to be full of vague and speculative claims, but he continued to take very seriously the possibility of mechanisms for the inheritance of acquired characters. In the third edition of *Elemente* (1926) he radically reworked and extended the last chapter with a thorough analysis of the most recent discussions. In this respect he was typical of continental European genetics in the interwar period in contrast to Anglo-American genetics.[20]

The nature of the 'gene'

In Johannsen's theory, genotype was the basic concept and genes had a derivative status. The genotype could not be exhaustively analysed into a structure of genes, i.e. the kind of hereditary factors that were investigated in the hybridization experiments of Bateson and even mapped on the chromosomes by the Morgan school. There was in Johannsen's view more to the genotype than being composed of such genes. In this sense he was a holist. The term 'gene' ('Gen') was proposed by Johannsen in his *Elemente* of 1909 as an abbreviation for 'pangene':

> Das Wort Gen ist völlig frei von jeder Hypothese; es drückt nur die sichergestellte Tatsache aus, dass jedenfalls viele Eigenschaften des Organismus durch in den Gameten vorkommende besondere, trennbare und somit selbständige 'Zustände', 'Grundlagen', 'Anlagen' - kurz, was wir eben Gene nennen wollen [p. 124].[4]
>
> [Author's translation: The word gene is completely free from any hypothesis; it only expresses the established fact, that at least many properties of an organism are conditioned by special, separable and thus independent 'conditions', 'foundations', 'dispositions'...]

In my reading there was a deeply realist tone to Johannsen's 'gene' already from the introduction of the term. Genes are given as empirical facts independently of what theories (hypotheses) we prefer when accounting for their nature. The realist understanding is confirmed by his characterization of genes in the third edition of *Elemente*. Genes are real entities which have been shown to exist. They are not merely hypothetical, like the gemmules, biophores and pangenes of earlier investigators:

> Wie es in diesen Vorlesungen vielfach hervorgehoben wurde, sind die Gene Realitäten, nicht hypothetische Komzeptionen, wie so viele früher in spekulativer Weise aufgestellete Einheiten, z. B. DARWINS gemmules, WEISMANNS Biophoren bzw. Determinanten, DE VRIES' Pangene (ursprünglich 1889) u. a…[p. 640].[5]
>
> [Author's translation: The genes are realities, not hypothetical conceptions, like so many entities that have previously been presented in a purely speculative manner like Darwin's gemmules, Weismann's biophores, de Vries' pangenes, (first time 1889) etc.]

I take Johannsen to claim that the evidence obtained through Mendelian hybridization and pure line selection experiments was sufficient to give some genes the status of facts. This was the case already in 1909 and of course much more so in 1926. Nevertheless, his 1926 chapter ends modestly with a statement that genes are still for us mostly 'entities of calculation, expressions of realities of unknown nature, but with familiar effects'.

There is strong continuity in Johannsen's view of the relationship between evolution and genetics from 1903 on. He was critical of theories of re-imprinting (neo-Lamarckism) and 'successive selection' (orthodox Darwinism) and saw investigations of the mechanisms of mutation and hybridization as the road to further progress. His own selection experiments were instrumental in establishing the stability, or 'hardness' of genotype and genes; and the combination of cytological analysis with breeding experiments pursued by the Drosophila school of Thomas Hunt Morgan was a main key to further progress. Johannsen was highly impressed by their experimental development of the chromosome theory.

Already in the second edition of the *Elemente* there was a long footnote discussing Morgan's chromosome 'hypothesis' [p. 605].[21] Johannsen appreciated the 'playfully elegant' use of Janssen's 'Chiasmatypie', not much different from Weismann's speculations. However, the excellent experimenter Morgan presented his ideas 'without any pretension'.They were simply an expression of his 'urge for "deeper understanding"'. Johannsen appreciated the working hypothesis as long as it was reined in by strict demands for factual empirical evidence. By the mid-1920s Johannsen found that the promises had been brilliantly honoured. In the preface to the third edition of *Elemente* he was very content that the 'ingenious theory of Morgan' on the whole is in 'beautiful harmony' with the views he himself had promoted from the first edition on. Briefly, the selection experiments of the genotype theory and the hybridization experiments of the chromosome theory had continued to supplement and support each other beautifully, in further confirmation of Johannsen's 'modern view of heredity' heralded in December 1910.

Genetic holism

Johannsen was not in doubt that the discoveries that the Morgan group made in the 1910s and 1920s represented a major advance. But he also saw radical limitations for a chromosome theory that aimed at analysing the whole genotype into independently existing genes. His critique was briefly and polemically formulated in a 1923 paper, 'Some remarks about units in heredity'. Besides the genotype paper of 1911, it is his only paper in English.

According to Johannsen, contemporary genetics was concerned with 'such genotypical units as are separable', but 'by far the most comprehensive and most decisive part of the whole genotype does not seem to be able to segregate into units. . .' He continued:

> Personally I believe in a great central 'something' as yet not divisible into separate factors. The pomace-flies of Morgan's splendid experiments continue to be pomace-flies even if they lose all 'good' genes necessary for a normal fly-life, or if they be possessed with all the 'bad' genes, detrimental to the welfare of this little friend of the geneticists [p. 137].[6]

To Johannsen, genes were entities that could be distinguished through the analysis of results from hybridization experiments. Whether such genes could also meaningfully be distinguished or separated as material entities (perhaps a kind of chemical molecule) was still uncertain. It would demand methods quite different from crossbreeding. In any case it should always be remembered that 'the characters of the organisms—their phenotypical features—are the reactions of the genotype *in toto*', he insisted [p. 139].[6]

Till the end of his life, Johannsen stressed the limitations of the new experimental science of heredity that he had helped to get going: the deeper causes of differences between higher taxa, class, family and genus had not really been touched on. Chromosome constitution in terms of genes cannot be the sole answer, he argued. For instance, the role of the protoplasm was almost unknown. All that had been investigated so far was relatively small differences and numerous larger or smaller abnormalities. Concerning the big question about 'the origin of species', genetics had so far contributed almost nothing, concluded Johannsen in a scholarly review of 'one hundred years of research in heredity'. But even these limited results were highly relevant to current theories of evolution. They implied annihilating criticism both of Darwin's idea of selection and of Lamarck's idea about inheritance of acquired characters. Sighed Johannsen: 'If genetics has not contributed anything positive to the 'theory of descent', it has at least cleared the ground of false ideas' [pp. 102–103].[7]

According to Johannsen's holistic approach, the fundamental concept is the genotype rather than the gene: 'Everything depends on the genotypes of the involved individuals' [p. 103].[7] And the genotype is not exclusively bound to the nucleus, or the 'genome' as today's terminology goes. It is a property of the whole organism. In this way Johannsen's genotype theory has much in common with modern systems theory as sketched, for example, by Denis Noble.[22] But in distinction to some trends in systems theory he insisted on a fundamental role for the genotype and its abstracted parts, the genes. He does not fit a parity thesis that other parts of the organism can fill the same role as genes, as causes of its development and reproduction. However, Johannsen emphasised the heuristic power of reductionist physico-chemical methods, as demonstrated for example by the success of the chromosome theory of Morgan and his co-workers.

Johannsen's genotype theory belonged to what Jonathan Harwood[20] has called the 'comprehensive' biological style of inter-war continental Europe as opposed to the 'pragmatic' Anglo-American style which was more narrowly focused on phenomena of inheritance. From the founding of genetics in the early 20th century, this comprehensive style inspired criticism of views that exaggerated genetic determination and neglected the role of environment. The historiography of genetics since World War II has largely neglected this alternative tradition. This tendency is expressed for instance in a disdainful attitude to any idea about inheritance of acquired characters. The biased treatment of Lysenkoism is an example. [23] With recent disintegration of the classical gene and new discoveries in the area of epigenetics,[24,25] historiography is also changing.

Johannsen's genotype theory may also provide some help in judging the possible implications of 'epigenetics'. If epigenetics is understood as the molecular processes of cellular differentiation in individual development, changes that are reproduced through mitosis,[26] this does not affect the genotype. Such processes belong to the formation of the phenotype. What Johannsen demonstrated so well in his bean selection experiment of 1903 was a striking stability of biological type—he sometimes used the term 'elementary species'—in a hereditary homogeneous population under normal conditions. In 1909 he introduced the term genotype to represent this idea of 'hard heredity', which became a basic principle in classical genetics. Heredity is generally stable and changes only intermittently. There is no continuous change of heredity as assumed in orthodox Darwinian or neo-Lamarckian theories. Johannsen explained genotype as the 'inner constitution' of the individual organism given by the fusion of egg and sperm in the zygote [pp. 612–13].[18] This constitution is ahistoric in nature, he insisted. It is independent of the history of earlier generations, analogous to the constitution of chemical substances like water (H_2O) or hydrochloric acid (HCl). Depending on circumstances, the concrete properties will be quite different—like water, ice, and steam [p. 648].[18]

Nevertheless, the 'hard' aspect of the genotype theory was an empirical claim, open to testing and modification. Johannsen did not reject the possibility of some kind of Lamarckian effects, especially in the long run. In the last edition of his textbook *Elemente* (1926) he added about twenty pages on this topic to the final chapter. There was intense research attempting to substantiate such ideas in the early decades of the 20th century, especially in the

German cultural sphere; but Johannsen found that, when all results had been scrutinized and weighed, the genotype theory was so far without serious competition.

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