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Review articles

The gene in search of an identity

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> "'I can't believe that' said Alice. 'Can't you?' the Queen said in a pity tone. 'Try again: draw a long breath, and shut your eyes'.
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> Alice laughed. 'There's no use trying' she said, 'one can't believe impossible things'. 'I dare say you haven't had much practice' said the Queen. 'When I was your age I did it for half-an-hour a day. Why, sometimes I've believed as many as six impossible things before breakfast'" (Through the Looking Glass, as quoted in: R.B. Goldschmidt's Presidential Address to the 9th International Congress of Genetics, Bellagio, 1954).

Summary. The concept of the difference between the potential for a trait and the trait proper, i.e., between the genotype and the phenotype, became clear only during the first decade of the century, mainly through the work of Johannsen. Although Johannsen insisted on that the terms he coined were only helpful devices to organize data about heredity, it is obvious that they were bound from the beginning to the hypothesis that there was "something" in the gametes that could be rendered to analysis as discrete units. These units were the genes.

This reductionist yet materially non-committed attitude has been developed into what I called instrumental-reductionism: the genes were hypothetical constructs that were accepted "as if" they were real entities. The research program developed on such a concept was very successful, not least because this instrumental approach allowed maximum flexibility in the attachment of meaning of the genes. While most geneticists accepted one or another position of this flexible concept, others took more extreme positions. At the one extreme end of the conceptual continuum was the realist approach that argued that genes were discrete, measurable, material particles, and on the other end, the claim that the attempts to identify discrete units only led to hyperatomism of a holistic view appropriate to heredity.

The acceptance of the gene as a material and discrete unit, in the beginning of 1950s, opened the way to a deeper level of conceptualizing both its structure ("cistron-recon-muton") and function ("one gene—one enzyme"). The discovery of the structure of DNA finally offered a chemical-physical explanation to the geneticist's requirements of a material gene. Thus, within less than 20 years the gene has been established as a "sharply limited segment of the linear structure" that is involved in the structrue of a product or its regulation.

However, with turning of much of the attention to the eucaryotic DNA, it was necessary to accommodate the gene to an increasing flood of findings that did not tally with its concept as *a* discrete material unit. Without much heart-seeking among geneticists, the gene regained its role as an instrumental unit, or even as just an intervening variable, "a quantity obtained by specified manipulation of the values of empirical variables". Though this flexibility demonstrated again that "the most fruitful concepts are those to which it is impossible to attach a well defined meaning", it brought us also into a situation in which the same term has a different meaning for each group of scientists. In order to avoid the danger "to be scattered over the face of all the earth" because of lack of communicable language, it might be advisable to halt a little and reflect on the meaning of our concepts and their function.

Introduction

The "gene", like the "electron", has often been quoted as an entity that has been invented or discovered—according to the point of view of the speaker—by scientists in constructing their theories. To the modern philosopher a dichotomy of theoretical and observable entities is artificial and meaningless.

> "Our drawing of the theoretical-observational line at any given point is an accident and a function of our own physiological make-up, our current state of knowledge, and the instruments we happen to have available and, therefore, ...it has no ontological significance whatsoever" (Maxwell 1962).

When modern genetics was born at the turn of the century, investigators like August Weismann and Theodor Boveri had already insisted on the existence of a hereditary material in the gametes, or more precisely, in the chromosomes of the gametes. Following Mendel, genetics was also from its beginnings explicitly reductionist. This reductionism was not necessarily meant in the strict sense of the word, namely as a belief that all observation statements should ultimately be expressible in physico-chemical terms. Rather it conceived the observables as complexes that might be broken up, or reduced, into more basic or primitive components or units. The term "gene" was, however, introduced by Johannsen only quite late, towards the end of the first decade of the century.

The number of histories of genetics or various aspects of it has been increasing constantly, but to my knowledge only Carlson (1966) published a systematic historical study specifically devoted to the gene. Other aspects of the history of the gene have been explored by Obly (1974) in his study of "The Path to the Double Helix"; in histories of genetics written by some of the participants (e.g., A.H. Sturtevant, L.C. Dunn, and C. Stern); in the biographies of some of its heroes (T.H. Morgan, H.J. Muller); and in numerous papers in current journals on the history of science. This paper is not intended as another history of the gene. Rather it is an attempt to explore the usefulness of the concept of the gene in genetic studies of today, in view of its meaning and function in the history of genetics. I wish to examine the evolution of the

meaning of the "gene" as a concept. Is this theoretically conceived entity referring to something or to some function, or is it just an intellectual devide to organize data? Is it believed to be "there", like microbes, so that it only took the invention of better chemical and physical devices, like the gel-electrophoresis and the electron-microscope to make it "observable", or is it thought to be just a helpful theoretical concept, devised to represent in a condensed form a wider and more elaborate hypothesis or theory about hereditary material?

MacCorquodale and Meehl (1948) pointed to a distinction one has to make between hypothetical constructs and intervening variables, or between hypothetical concepts and abstractive concepts. Abstractive concepts or intervening variables are purely "summarizing" characters, they "neglect certain features of experience and group phenomena by a restricted set of properties into classes". An intervening variable is simply "a quantity obtained by a specified manipulation of the values of empirical variables: it will involve no hypothesis as to the existence of the observed entities or the occurrence of unobserved processes". Hypothetical constructs, on the other hand, encompass "words which are not explicitly defined by the empirical relations". In hypothetical concepts something is added to the empirical data, we add to the coordinated grouping of data "certain existence propositions, i.e., propositions that do *more* than define them". I shall endeavor to show that although the "gene" was conceived by Johannsen essentially as an intervening variable, it was, as one could expect, enmashed from the moment of its birth in hypotheses, i.e., it was a hypothetical construct. But becoming a hypothetical construct, did not mean that it was conceived as a "structure". While for much of genetics a heuristic of "as if there were genes" was a fruitful approach to a research program, there was from quite early on another research program aimed at isolating the corpuscular entities that were the genes.

Even though it would appear that with the discovery of the structure of the DNA the gene finally emerged as a concrete spatial structure, it was gradually realized that the "real" gene was only an abstraction. In the beginning the gene was conceived as a discrete, specific sequence of nucleotides of DNA involved in a specific function. It withstood well the adaptations required by further research up to the middle of the 1960s. By this time some felt that the major problems of molecular genetics were solved, and all that was left for geneticists to do was "to iron out the details" (Stent 1968).

However, with the shift in research focus to eucaryotes, the tables were soon turned over. Ever since Britten and Kohne discovered in 1968 the highly redundant DNA of eucaryotic chromosomes, it became increasingly clear that reference to "The Gene" as a discrete and concrete entity, could not be maintained. With each new development in molecular genetics, it became more obvious that the gene was nothing more than an intellectual device helpful in the organization of data. Perhaps more than ever before, the gene has gained a status of an intervening variable, construed by investigators according to their needs, rather than as a hypothetical, discrete unit along the chromosomes, or the DNA strands. Unfortunately, in this process the gene came to mean something different for different groups of research workers. In our excitement to exploit the baffeling achievements of modern genetic research, it might perhaps be wise to stop for a moment to sort out our concepts, lest our fate will be similar to that told in the book of Genesis:

> "And the Lord said, 'Behold, they are one people, and they have all one language; and this is only the beginning of what they will do; and nothing that they propose to do will now be impossible for them. Come, let us go down, and there confuse their language, that they may not understand one another's speech'. So the Lord scattered them abroad from there over the face of all the earth, and they left off building the city." (Genesis 11:6–8)

Phenotype versus genotype

Mendel in his classic paper of 1866 discussed the inheritance of "Merkmale"—which is translated into English as "characters": characters such as seed color or form, plant height, etc. Literally, the meaning of Merkmale is "markers". Thus, it may be argued that Mendel realized that his characters were actually only the external markers of the unobservable, yet real hereditary units. Indeed, as Iris Sandler (1983) pointed out, Mendel actually talked of elements of the cells that carried "potentials" of the traits:

> "In our experience we find everywhere confirmation that constant progeny can be formed only when germinal cells and fertilizing pollen are alike, both endowed with the potential for creating identical individuals, as in normal fertilization of pure lines" (Mendel 1866).

Darwin's misconceptions about the role of heredity had been frequently discussed, even in his own time (see, e.g., Jenkin 1867). But it appears that it remained for Johannsen, towards the end of the first decade of Mendel's rediscovery, to explicate—with the aid of the terms he coined, namely the "genotype" and the "phenotype"—the difference between the potential for a trait and the trait itself and thus expose Galton's misconceptions.

At the end of this book "Origins of Mendelism", Olby speculates on what would have happened had Mendel, on his visit to London in 1862, met Galton: "The history of genetics would surely have been different had these two original thinkers met" (Olby 1966). I doubt whether Johannsen would have agreed with this conclusion. The philosophies of these two men were too different for the gap to be abridged, surely not in a brief single meeting. Galton, like his cousin Darwin, was thinking of nature in synthetic terms, while Mendel's approach to the problem of heredity was a strict analytic one.

On the face of it, it did appear that Galton was in a position to realize that it was possible to distinguish between the hereditary and the environmental components of variability, and thus to differentiate between the potential for a character and the character proper. Indeed, in his 1872 paper "On blood relationships" Galton showed what seems to be a reductionist insight into the difference between the character and its hereditary basis:

> "Each individual may properly be conceived as consisting of two parts, one of which is latent and only known to us by its effects on his posterity, while the other is patent, and constitutes the person manifest to our senses. The span of the true hereditary link connects... not the parent with the offspring, but the primary elements of the two, such as they existed in the newly impregnated ova..." (Galton 1872).

Furthermore, Galton had the insight that one could reduce the problem of inheritance to one-trait-at-a-time. In his letter to Darwin on October 19, 1875, he wrote: "let us deal with a single quality, for clearness of explanation..." As a matter of fact, he even discovered the law of segregation when he show-

ed how the intermediate coat color of hybrids could be maintained by assuming that the "organic molecules" of heredity segregated (Olby 1966).

Yet, Galton did not purpose his reductionist insight, in spite of his awareness of the particulate structure of matter. On the contrary, Galton as well as his cousin Darwin, were concerned with laws that may explain the function and the structure of the whole, without being distracted by the rules that may govern the parts. Their approach was strictly a synthetic one. Both endeavored to find the "law of large numbers" for natural phenomena. Darwin adopted the blending theory of inheritance in order to overcome the "irrelevant" deviations of individuals and to see the regularity of the total. Galton looked for the "stability of type" hidden behind the individual variability observed in characters such as intelligence or the circumference of pea seeds. He tried to "represent" whole populations, with all their variability, by few statistical parameters, like the mean and variance. The mean of the normal distribution was for him more than a methodologic parameter. It allowed the discovery of meaningful biologic concepts.

Mendel's breakthrough, on the other hand, was when he applied a reductional heuristics to the problem of heredity. His success was his ability to disregard the whole, to focus on one trait at a time, while ignoring all the residual variability of his peas. He reduced the problem of heredity to a *quantitative* analysis of *individual* qualitative characters.

When Mendel's work was finally raised from oblivion in 1900, the concept of a material of heredity, being different from the hereditary traits, was well established through the work of persons like August Weismann:

> "My present task is not to deal with the whole question of heredity, but only with the single although fundamental question—'How is it that a single cell of the body can contain within itself all the hereditary tendencies of the whole organism?' ... Either the substance of the parent germ-cell is capable of undergoing a series of changes which, after the building-up of the new individual, leads back again to identical germ-cells; or the germ cells are not derived at all, as far as their essential and characteristic substance is concerned, from the body of the individual, but they are derived directly from the parent germ cell. I believe that the latter view is the correct one... I propose to call it the theory of 'The continuity of the germ plasm', for it is founded upon the idea that heredity is brought about by the transference from one generation to another, of a substance with a definite chemical, and above all, molecular constitution. I have called this substance 'germ-plasm', and have assumed that it possesses a highly complex structure, conferring upon it the power of developing into a complex organism" (Weismann 1885).

Weismann's conclusion was: "the nuclear substance must be the sole bearer of hereditary tendencies".

Yet, in spite of the material separation of the hereditary material from the traits proper, and in spite of the application of the reductionist methodology to problems of heredity, it took almost another decade until the gap between Galton's quantitative synthetic conceptual world and the new concepts constructed upon the rediscovered Mendelian quantitative analysis, were clarified.

Johannsen, like Galton and contrary to Mendel, chose quantitative characters for his studies, i.e., the length and breadth of the bean seeds. His approach was, however, to treat them as if they were discrete characters. Upon analyzing his experimental results, he was able to show that although Galton talked of "each individual ... conceived as consisting of two parts, one of which is latent ... the other patent", he did not really comprehend the operational meaning of the difference between the potential for a "type" and the "type" itself.

The error may be traced back to Quetelet who measured the distribution of physical traits in populations of human beings and attempted to describe a population by a single characterising parameter, the mean. Johannsen (1909) writes:

> "Quetelet considered this concept of type to be of great importance. For this investigator the fact that the population of a given nation could be grouped according to the binomial distribution with respect to body length and many other measurable characters, was synonymous with proof that such populations were composed of a single type. In such cases the type was represented by the mean."

Thus, for Quetelet and Galton a bimodal distribution indicated random (= irrelevant) variation about two biologically meaningful factors, while a unimodal distribution indicated that only one biologic factor was involved.

While it is true that a bimodal distribution may be caused by random variations about two different means, the error of Quetelet, and that of Galton after him, was that they assumed the reverse to be also true, i.e., that a unimodal distribution indicated only one factor and that the random deviations about it were responsible for the distribution. Johannsen (1909) goes on:

> "However, a critical examination of the results of Galton will show us, that from the very good correspondence with the binomial distribution, absolutely no conclusion can be made on the presence of only one type. If we take the progeny [of the subpopulations that Johannsen extracted from Galton's data] as a whole, we will find that the individuals of the three types that had been detected, group quite neatly around just one single type".

and he adds:

> "The 'type' in Quetelet's sense is thus only a statistical concept... It is only an illustration of pure descriptive nature. Nothing can be said in advance about the important question whether such a type is uniform or whether it conceals the presence of groups of different nature. This problem can be solved, as a rule, only through studies of heredity"[1].

1 At this place Johannsen made a mistake analoguous to that of Quetelet and Galton. In his first example he examined the progeny of three subpopulations of Galton's: progeny of tall parents, progeny of small parents, and progeny of parents of intermediate height. He convincingly showed that, although the three subpopulations of progeny had different means, the pooled data presented a smooth, unimodal (binomial) distribution. But then he gives an inverse example: he examined the F_2 of a mating between his long and short beans. The distribution of lengths of these beans fitted very well that expected from a simple binomial distribution. Yet, Johannsen argued, this statistically uniform population was actually a mixture of three subpopulations, the short type, the long type, and the hybrid type. To demonstrate this he presented a table in which he had divided his population into three subpopulations presumably by length, and then gave the length distributions and the statistical parameters for all three progeny subpopulations. However, this is wrong: he could not separate the population into three subpopulations on the basis of length differences. There is no way to assign a sample of beans of a *given* length to three different subpopulations on the basis of ... length. He must have divided the progeny into three subpopulations on the basis of some other trait, such as the color of the seeds, that characterized the parental long and short bean lines. Pooling these subpopulations to give a unified distribution can be reversed only when there exists an independent marker to make the distinctions

Thus, Johannsen named Quetelet's and Galton's "Typus"—which was only a type-in-appearance—"phenotype". On the other hand, the hereditary unit of variability—deduced from biologic, not statistical considerations—he called "gene",[2] and he explicated what he meant by this:

> "Only the simple conception should be expressed, that a trait of the developing organism is conditioned, or may be partly determined, through 'something' in the gametes".

East (1912) interpreted it this way:

> "The difference between Galton's law and Mendel's law is that the true criterion of the germ plasm of any individual is its breeding *power* and not the somatic appearance of its ancestry".

Johannsen's experiments, in which no genotypic variation was detected in the inbred lines of beans over many generations, bolstered the concept of the constancy of the genetic material. He did not commit himself, however, towards the *material* basis of heredity, or its unit—the gene. He talked about "something" ("Etwas") that was present in the gametes and the zygote, but contrary to Weismann, he made the point that his terminology was not committed to any specific conception of the nature of the gene. As far as he was concerned he believed it to be a term without a hypothesis: "No hypothesis about the nature of this 'something' should thereby be constructed or supported". And he went on and insisted that no hypothesis was *necessary* for the persuit of research in heredity:

> "No certain idea about the nature of the 'gene' is at present well enough established. This, however, is of no consequence to the efficiency of research of heredity. It is enough that it can be asserted with certainty that such 'genes' are available" (Johannsen 1909).

Not only did Johannsen refrain from assigning any material basis to the genes, he was even skeptical as to the reality of the genes as meaningful beyond their operational usefulness. Indeed, in the third edition of his book, published in 1926, he saw fit to add a section in which he acknowledged the debt Mendelians owed to reductionist heuristics introduced in the nineteenth century into biologic research. But, at the same time, he expressly dissociated himself from their structural kind of reductionism. For him the breakdown of the whole structure was as artificial and naive as functional reductionism:

> "The great physiologist Claude Bernard wished already in 1878 to make a sharp distinction between the concerted interplay of completed organs of the bodies of animals, and their supposed independence in development, similar to the manner in which the different parts of a rifle are produced independently of each other in the factory'! But, it is not always easy to distinguish conceptually between organs, body parts, features, and characteristics (which are often organ-conditioned). In short, it is often difficult to separate morphological, rather localized 'markers', from the physiological, more diffuse, ones. The speculative projection of elements of such a descriptive dismembering of the organism, unto the constitution of the corresponding gametes, is actually an expression of a quite naive way of thinking" (Johannsen 1926).

Thus, although the concept of the gene was established with the good intention to be just an "intervening variable", it had already from the beginning a value added to it, this "Etwas" that Johannsen was talking about. As Woodger (1967) points out, our concepts "are constructions in thought representing historically an immense amount of intellectual work". Thus the hypotheses come to us before, rather than after we made our observations. As a matter of fact it is the preconceived hypothesis that makes the observed phenomena meaningful.

Notwithstanding his intentions Johannsen's gene was after all a "hypothetical construct". I would like to call this approach "instrumental reductionism", and hope to show that this logically inconsequential approach provided the concept that wide range of flexibility, that was important for its maintenance.

The instrumental gene

Mendelian reductionism implies that a gene is that "something" which is the potential for a trait. But how do your recognize a gene? By its "representative", the trait, or more accurately, the alternative appearances of the trait. The only way to identify genes was by their effect. What is a trait (or variation in a trait) that defines a gene? Mendel judiciously chose traits with clear-cut differences: yellow as opposed to green, wrinkled as opposed to smooth, tall as opposed to dwarf. But most characters cannot be delimited this way. How do you determine then, what is a "unit character" that stands for a "unit factor"? The answer of the Mendelian was simple: that trait that "Mendelizes" is by definition determined by a single gene, or in Castle's (1919) words: "any visible character of an organism which behaves as an indivisible unit of Mendelian inheritance" determines a unit-factor or a gene. Once one accepts this *definition* one can ignore the unit-character, and refer to the genes that are presumed to stand behind them: we observe the characters or traits, but these are only the "markers" for the genes. If a trait or a character does not "Mendelize", by this definition it is controlled by more than one gene.

> "[Castle's] experimental studies of heredity, begun in 1902, early led [him] to observe characters which were unmistakenly changed by crosses and so [he has] for many years advocated the view that the gametes are not pure in the sense expressed by Bateson" (Castle 1919).

Such a view was rejected, as Castle pointed out, not because something was wrong with his experimental procedures, but on the ground that it was not "in harmony with the results of Johannsen and other investigators".

Upon Muller's confidence that in no known case do the variations of a gene among the immediate descendents of an

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2 From the examination of the 1905 Danish edition of Johannsen's book, *Arvelighedslaere,* it is obvious that the *concept* of the phenotype and the genotype were already clear to him in 1903 when he gave his lectures on which the book is based. He even tried to coin a name for what became later known as phenotype—"Livs Type", that is, Life Type. For what became later the gene he still used the term "Anlaeg", that is, *Anlage.* In free English translation: "These number types, as we may call them, are pure statistical, pure calculational terms. The types of organisms, in contrast, could be called biological types, or in a short word, 'life types'. There could never have been any doubt that the sex cells contain something that is an essential determinant for the character that develops. This 'something' we call Anlage. So far we do not have a certain idea about the nature of it, but this is of no consequence. By adhering so far to the simple character we could be satified in saying that the life-type is a character or a trait, behind which there is a certain Anlage. The specific traits of an individual are not determined exclusively by the Anlage that was present in its parents' sex cells, but also by the conditions under which its development took place." (See also the discussions of F.B. Churchill (1974), William Johannsen and the Genotype Concept, Journal of the History of Biology 7:5–30)

individual possessing it, form a normal distribution of variants about the original type (Muller 1914), Castle points out that,

> "The use of the word 'gene' in Muller's sweeping statement safeguards the author, since no one, so far as I know, claims ever to have seen a 'gene' or to have measured it. How could the 'variation of a gene' be expected to 'form a probability curve' if the gene is not measurable?" (Castle 1915).

Yet, it was probably not his experimental results with the piebald rats that finally convinced Castle in 1919 to give up his resistance to the constant-gene concept: these experiments could have easily been interpreted on his previous assumption of the modification of units in heterozygotes. Rather, as Castle admits, his results

> "offer *no obstacles* to the *proposition* of Johannsen (ably supported by East), that a gene *terminology* is adequate to express all known varieties of inheritance phenomena" (Castle 1919) (italics mine).

Ably, indeed, was East's presentation of the case for the instrumental reductionist concept:

> "As I understand Mendelism it is a concept pure and simple. One crosses various animals or plants and records the results. With the duplication of the experiments under comparatively constant environments these results recur with sufficient definiteness to justify the use of a notation in which theoretical genes located in the germ cells replace actual somatic characters found by experiment... Mendelism is therefore just such a conceptual notation as is used in algebra or in chemistry" (East 1912).

Once admitting that the term unit-factor (gene) is a conceptual device, we should be aware of its limitations as a descriptive term of "reality":

> "...we have not pulled something new and astonishing out of the germ cell, we remember that a unit factor represents an idea and not a reality, though it must have a broad basis of reality if it is to describe a series of genetic facts.
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> ...We know nothing of this germ cell beyond a few superficial facts, but since a short description of the breeding facts demands a unit description, the term factor unit has been coined. As I hope to show, a factor, not being a biological reality but a descriptive term, must be fixed and unchangeable. If it were otherwise it would present no points of advantage in describing varying characters" (East 1912).

Lest East's instrumental reductionism be misunderstood as rejecting the material basis of heredity, he added a footnote:

> "...The term factor represents in a way a biological reality of whose nature we are ignorant just as a structural molecular formula represents fundamentally a reality, yet both as they are used mathematically are concepts" (East 1912).

East is aware of the instrumental significance of the gene: It is there to do a job. If it does not do its job, there is no use keeping it!

> "How far may we carry this conceptual notation? My answer is: just as far as the notation interprets the facts of breeding and is helpful...
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> "I do not believe that biologists have sufficient facts as yet to warrant any concrete meaning being given to their notation as regards germ-cell structure, but I do maintain that the Mendelian notation satisfies the facts of size inheritance as well as it satisfies the facts of qualitative inheritance. As a description it goes the whole way. If qualitative inheritance is Mendelian, quantitative inheritance is Mendelian; if quantitative inheritance is not thus described, qualitative inheritance is described not a whit better" (East 1912).

Castle was not wrong in the interpretation of his experimental results, his interpretation was not helpful, not instrumental. It did not allow the expected generalizations to be made. Castle's "unit character" was more of the nature of an intervening variable, an abstractive concept for which the truth of the empirical laws constituted not only the necessary but also the sufficient conditions. East finally convinced him that the "unit factor"—or the "gene"—was a hypothetical construct, for which the empirical laws were necessary, but not sufficient! This concept of the instrumental reductionist gene has been maintained and proved extremely successful for many aspects of genetical research ever since.

When Vogel (1970) infers that a monogenic autosomal dominant mode of inheritance is responsible for the low electroencephalogram pattern he studied, he is not worried about a material segment of DNA that may be correlated with this function, as long as he can persue the analysis at the level of "as if" there was such a material gene somewhere. In fact, he would probably not be surprised if further investigation will show the trait to fit better a model of two genes, since we know that the expectations from such a model are "alarmingly similar" to those of a simple autosomal-dominant mode of inheritance (Vogel and Motulsky 1982). On the other extreme of the same continuum are the genetic studies of quantitative traits, such as those of Morton et al. (1970). They assume the function of many discrete genes, although it is usually not only impossible but also unnecessary to refer to the individual genes and their specific phenotypes. Not only is there no (material or proverbial) gene for a trait such as "skill", but the theory assumes that "skill" is determined by many, equally effective, and therefore also interchangeable genes. The enumeration of genes in such analyses has only an operational value in the narrow sense.

Once the concept of multigenic traits was introduced by Nilsson-Ehle, Emerson, and East, it was also possible to resolve the old dispute with the Galton-Pearson school. Galton accurately interpreted the correlations between traits of parents and their offspring, between sibs, and especially between twins as a measure of the genetic component of the variation in the traits that were considered. It was Fisher's (1918) statistical analysis that showed how the theory of multiple Mendelian genes, segregating in the populations, could be applied to these correlations between relatives. Without indentifying specific genes it was possible not only to estimate the genetic component in the total variance of traits, but also to get estimates of the degree of dominance of the presumed genes, on linkage between them, and on the number of genes that must be presumed to be involved. Once this was appreciated, the way leading to the reconciliation between Darwinists and Mendelians was opened. This culminated in the establishment of the Synthetic Theory of Evolution, or neo-Darwinism.

The concept of multiple genes did not mean that it was impossible to break complex quantitative traits up into simpler ones. Often, when a complex trait was studied more thoroughly at the phenotypic level, it has been possible to identify discrete phenotypic units within it, and to relate these unit-characters to unit-factors or specific genes (see e.g., Motulsky 1982). It is the power of instrumentalism that it does not accept an analysis as final, but only as a provisional device until another, better one, is advanced.

To stress the fruitfulness of this approach suffice it to mention that under the auspicies of the instrumental reductionist concept not only the chromosomal theory of genetics was established, but also the linear maps of the genes were inferred and found to be isosequential with the cytologic maps of the chromosomes. So much so that when T. H. Morgan discussed in his Nobel Lecture in 1933, "What are genes?", he could state:

> "Now that we locate the genes in the chromosomes are we justified in regarding them as material units; as chemical bodies of a higher order than molecules? Frankly, these are questions with which the working geneticist has not much concerned himself, except now and then to speculate as to the nature of postulated elements. There is no consensus of opinion amongst geneticists as to what genes are—whether they are real or purely fictitious—because at the level at which the genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle" (Morgan 1933).

This instrumental approach of Morgan, however, was fruitful only because of the ever-present competing realist philosophy that—by providing the discrete, material gene concept—suggested to the instrumental geneticists a meaningful experimental strategy, without committing him to a specific entity called the gene.

The material gene

When Muller attacked the operational interpretation that Castle gave to his breeding experiments with rats, he had more in mind than East's instrumental gene concept. Like East, Muller too pointed out that, since the results of Castle were explicable in terms of "multiple factors", this interpretation should be applied. But whereas for East the genes were theoretical units that "replace actual somatic characters found by experiment", for Muller they were units in their own rights, with inherent characteristics that could be specified, even though the only way to recognize their presence, for the time being, was by their effect.

> "Besides the ordinary proteins, carbohydrates, lipoids, and extractives, of their several types, there are present within the cell *thousands* of distinct substances—the 'genes'; these genes exist as ultramicroscopic particles; their influence nevertheless permeate the entire cell ... the genes are in the chromosomes ... The chemical composition of the genes, and the formulae of their reactions, remain as yet quite unknown" (Muller 1922).

The existence of discrete genetic units is already justified on purely rational considerations:

> "The gene has sometimes been described as a purely idealistic concept, divorced from real things, and again it has been denounced as wishful thinking on the part of those too mechanically minded. And some critics go so far as to assert that there is not even such a thing as genetic material at all, as distinct from other constituents of living matter.
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> However, a defensible case for the existence of separable genetic material might have been made out *on very general considerations alone"* (Muller 1947) (italics mine).
>
> "What is meant ... by the term 'gene' material is any substance which, in given surroundings—protoplasmic or otherwise—is capable of causing the reproduction of its own specific composition, but which can nevertheless change repeatedly—'mutate'—and yet retain the property of reproducing itself in its various new forms" (Muller 1926).

The gene has been reified. It has been conceived as a *spatial* structure. The gene is not any more *determined* through its phenotype. As a matter of fact, it *determines* the phenotype:

> "Though particulate in their self-reproduction, their products in the cell interacts in the most complicated ways, both with one another and with the products of environmental conditions, in determining the characters of organisms, contrary to what many early Mendelians had assumed. Their integration, however, is essentially one of the gene *effects* only, since in the immediate process of their autosynthesis they remain substantially independent" (Muller 1926).

As a corpuscular, spatially separable entity, the gene should be quantifiable. Indeed, from early on Muller published estimates of the number of genes on the chromosomes and of their size (Muller 1916), as well as attempted to determine their borders ("left-right-test" Muller 1956). Probably the most explicit attempt in this direction was the study of Timofeeff-Ressovsky et al. (1935). They considered the genes as discrete, quantifiable molecule-like units, amenable to chemical-physical measuring methods.

> "The integration of genetics with cytological research has shown that the gene, originally a simple symbolic representative for a Mendelian unit, could be localized in space and its movements followed. The refined analysis in *Drosophila* has led to estimates of gene sizes which are comparative to those of the largest known molecules ... when we speak of genes as molecules we are ... thinking ... more generally of a well-defined union of atoms than of chemically defined molecules".

Quite good estimates of the size of enzyme molecules and even of bacteria had been obtained by determining the amount of radiation energy necessary to inactivate them: the larger the targets, the more radiation energy was needed to achieve inactivation. Once genes were envisaged as molecule-like units, it was a straightforward consequence to extend the energy target-size theory to genes, i.e., to measure the size of the genes by the energy required to induce a lethal mutation in an average gene.

I wish to maintain that it was the combination of this material approach on the one hand and the instrumental one on the other that was critical. It was the dialectic of the two philosophies, that of Muller, seeing a theory as a "projected map" of reality, and that of East and Morgan, seeing theory as a premise providing nothing more than the "principles of mapping" (Nagel 1968) that secured progress. Our analysis of the genetic system started from the trait. We envisaged traits to be due to the function of hypothetical constructs, the "genes". This instrumental approach has been, and still is, extremely effective. But once we turned the hypothetical construct into a material entity, it was possible to progress to another level of analysis of the function of these entities. This is exactly what Beadle and Tatum did at the beginning of the 1940s. They concluded that

> "Since the nature of the organism *depends* on the properties of the genes in the undifferentiated cell from which it develops, it may be *assumed* that genes in some way control the reactions both as to their kind and their time relations" (Beadle and Tatum 1941a) (italics mine).

Considering the limitations that the physiologic geneticist usually encounters on attempting to determine the physiologic and biochemical bases of already known hereditary traits they were

> "... led to investigate the general problem of the genetic control of developmental and metabolic reactions by reversing the ordinary procedure and, instead of attempting to work out the chemical basis of known genetic characters, to set out to determine if and how genes control known biochemical reactions. ... The procedure is bassed on the assumption that X-ray treatment will induce mutations in genes concerned with known specific chemical reactions. If the organism must be able to carry out a certain chemical reaction to survive on a given medium, a mutant unable to do this will obviously be lethal on this medium. Such a mutant can be maintained and studied..." (Beadle and Tatum 1941b).

The concept of the material gene suggested a new, deeper level of analysis of function that was condensed into the well known slogan: "one gene—one enzyme".

In a similar manner the establishment of the material gene concept suggested a deeper level of analysis into the structure of the gene itself. Lewis, Pontecorvo and, finally, Benzer were able to show that what was considered to be the material gene, a unit of function, recombination, and mutation, was actually three different entities. These were the largest functional unit that was defined by the cis-trans test ("cistron"), the smallest recombination unit ("recon"), and the smallest unit that could mutate ("muton") (Benzer 1957).

The non-reductionist concept

While the realist concept of the gene may be envisaged as an extreme view on the instrumentalist continuum of possible hypothetical constructs, Goldschmidt's views may be considered to represent the other extreme end of this continuum. For him genes were abstractions, intervening variables that had been helpful in organizing observations at the early days of genetics, but not any more.

> "Now to the two philosophies of genetics to be considered. One is the statistical, or static point of view; the other the physiological, or dynamic point of view. ... The statistical basic philosophy tries to interpret every generalized set of facts by the introduction of more and more units for statistical treatment. ... It tries to explain all basic features of genetic phenomena by introducing more genes... In this way a system is finally established, ... which I must call hyperatomism...
>
> Although the physiological approach accepts, naturally, the basic statistical tenents of genetics, it tries, actually within the rule of parsimony, to avoid looking for explanations in terms of unproved, additional systems of units for more and more genic permutations" (Goldschmidt 1954).

Like Muller, Goldschmidt saw in the elucidation of the nature of the gene, the central problem of genetics: "As long as genetics has existed, the ultimate problem has been the nature of the gene, its reduplication and mutation" (Goldschmidt 1950), but he denounces Muller's reductionist philosophy. Goldschmidt saw in the whole chromosome the "real" unit of structure. Experimental data pointed at loci along the chromosomes. But adding to these observational correlates any assumptions on their reality was "hyperatomism", which was for Goldschmidt not only superfluous, but even destructive.

One of the most bitter disputes between Goldschmidt and Muller was that over "position effect". Sturtevant had discovered that the expression of genes might depend on their neighbors along the chromosomes. He called the phenomenon "position effect". For the discrete gene concept this phenomenon posed a challenge that has not been solved satisfactorily to date. For Goldschmidt the meaning of position-effect was obvious:

> "The conclusion, then, is that gene mutation and position effect are one and the same thing. This means that no genes are existing but only points, loci, in a chromosome which have to be arranged in a proper order or pattern to control normal development. ... We might of course call a change of arrangement at a locus, a gene. But then there are no genes in the normal chromosome, and the mutant gene has no wild type allele, as the whole wild type chromosome is the allele for all mutant genes in the chromosome" (Goldschmidt 1938).

On the other hand, it was just Goldschmidt's nonreductionist concept that blocked his way to reach a deeper level of understanding of what he called "the physiological, or dynamic point of view": We have seen how the instrumental reductionist concept led Beadle and Tatum, through the material gene concept, back to a new insight into gene function. Contrary to Goldschmidt who claimed that "the mutant gene has no wild type allele", the "one gene—one enzyme" attitude allowed Beadle and Tatum to deduce the function of the wild type allele directly from that of the mutant allele. This was also the approach adopted by Garrod already in 1908, when he introduced the concept of "inborn errors of metabolism". Garrod's insight was, however, too much ahead of his time: it needed the development of the mediating concept of a material gene to reach from one functional level to the other.

With the recent developments in molecular genetics, when the discrete genetic unit lost much of its glance, when genetic units are known to overlap, and functional units were found to be organized in hierarchial systems, there are people who try to revive Goldschmidt's "non-reductionism". For these it is best to quote Goldschmidt's own words:

> "There were ... biologists who opposed the theory of hereditary units on general grounds. They had to disregard all known facts of genetics in order to prove their point and were therefore in the wrong even if it should turn out now that their sterile scepticism in the face of overwhelming facts had happened to put them after all on the right side" (Goldschmidt 1938).

The DNA gene

The realist concept of the gene, leading to a deeper insight into the gene's function ("one gene—one enzyme") and structure ("cistron"—"recon"—"muton") culminated in Watson and Crick's discovery of the structure of DNA. That nucleic acids were the core of the hereditary material, was actually known already at the early 1920s, from the work of Griffith on transformation in pneumococci. What was needed was a physico-chemical understanding of the organization of these nucleic acids that would correspond to the conceptual framework of genetic research. Watson and Crick specified from the beginning how the model of DNA that they presented answered these demands:

> "A structure ... which ... immediately suggests a mechanism for self-duplication.
>
> Though the sugar phosphate backbone of our model is completely regular ... any sequence of pairs of bases can fit into the structure. It follows that in a long molecule many different permutations are possible, and it therefore seems likely that the precise sequence of bases is the code which carries the genetical information.
>
> ... spontaneous mutations may be due to a base occasionally occurring in one of its less tautomeric forms" (Watson and Crick 1953).

Thus the Watson-Crick model gave a chemical answer to the geneticists' requirements of the material gene: (a) It was cap-

able of self-replication. (b) It was a basically homogeneous structure that allowed enough variability to code for many different and specific products. (c) Mutations could occur, and could be perpetuated just like the original version.

The fundamental unit of molecular genetics became the nucleotide. Molecular geneticists assumed that now the gene was "relegated to the role of a secondary unit aggregate comprising hundreds or thousands of such nucleotides" (Stent 1970). For a time it was believed that Benzer's units of mutation and recombination were nothing more than single nucleotides along the DNA molecule. Indeed, the terms muton and recon disappeared from our glossary (as it turned out this was premature: neither the unit of recombination, often not even the unit of mutation, correspond to single nucleotides). But even molecular geneticists needed a "meaningful" functional unit of DNA. So that after a short eclipse in which the use of the term "gene" fell out of grace, the "cistron" was identified with the "gene". The material gene was established as a discrete, continuous segment of DNA: "each cistron corresponds to a sharply limited segments of the linear structure" (Benzer 1959). The gene was a segment that, operationally, could be identified by its polypeptide product, but it was a discrete segment in its own right, independently of whether it was transcribed and whether the transcript was translated. When it turned out that some specific and discrete segments were transcribed but not translated (rRNA and tRNA genes) and that others were not even transcribed ("pseudogenes"), these findings could be adjusted on the instrumental level, as long as they did not affect the concept of the material gene. "One gene—one enzyme" had not to refer just to an enzyme. It was the gene that was "there", and when the product was composed of several polypeptides of genetically independent origin, the slogan was easily adapted to become "one cistron—one polypeptide".

When Jacob and Monod discovered that some discrete segments of the DNA strands were involved not in the specification of any product, but rather in the regulation of the production of other segments, it was not difficult to extend the concept: there were "structural genes" and there were "regulatory genes". The concept of well defined DNA sequences that could be related to specific functions was maintained. But which was now the structural gene? The segment of DNA that was transcribed as *one* unit into RNA was translated into *several* distinct specific polypeptides. Which was now the gene? The unit transcribed into one RNA, or perhaps that which was translated into one specific polypeptide? A strict adherence to the realist concept of the gene, as the most basic unit of inheritance, would have demanded that the transcribed unit would be the gene. A strict adherence to the instrumental formulation of an entity that best corresponds to observable properties, would have demanded the unit of translation to correspond to the gene. The unit of transcription became the "operon" and the name "cistron" was reserved for the translational unit. This pragmatic solution may signify the beginning of the reversal of the process, back from the well defined discrete material gene, to the abstraction:

> *"Of course* we have to simplify and abstract, and anatomy represents *one* way of doing this in regard to living organism—one mode of abstraction. ... when we come to interpret the results synthetically, we forget their abstract nature, then we fall into the 'fallacy of misplaced concreteness'..." (Woodger 1967).

The fact is that geneticists did not fall into this fallacy of concreteness, but rather started a pragmatic retreat from the material gene concept to the instrumental concept. This was not always appreciated among the persons involved, primarily among the molecular biologists, but also among some historians. Thus writes Olby (1974): "It has often been remarked that until the emergence of biochemical genetics from obscurity in the 1940s geneticists worked in conceptual vacuum. To be sure, they had the character, the gene, the allele, the locus and the chromosome map, but what was on the map? Genes? what *are* genes, and what is the causal sequence connecting the gene with the character it determines?"

As to many molecular geneticists, towards the middle of the 1960s, there was a strong feeling among them, that within less than two decades they "rescued" the gene from the biologists, and successfully accomplished the task of reducing genetics to the physico-chemical level. The gene referred to a real entity, which was nearly completely interpreted. The "instrumental scafolds" could gradually be dismantled. All the basic problems have been solved, even though it was still necessary to "iron out the details" here and there. This is the way a molecular biologist saw the task and its accomplishment:

> "The fundamental unit of classical genetics is an indivisible and abstract gene. In contrast, the fundamental unit of molecular genetics is a concrete chemical molecule, the nucleotide, with the gene being relegated to the role of a secondary unit aggregate comprising hundreds or thousand of such nucleotides...
>
> by the mid-1960s the general nature of both autocatalytic and heterocatalytic functions of the DNA was understood... The real core of genetic theory was lifted from the deep unknown in which Muller had found it to lie only fifteen years earlier. We now *do* have actual knowledge of the mechanism underlying that unique property which makes a gene a gene: Formation of complementary hydrogen bonds seems to be all there is to how like begets like" (Stent 1970).

Stent is, however, disappointed:

> "Alas, the very success of molecular genetics in explaining one of the most profound mysteries of life in terms of workaday chemical reactions altered the spiritual qualities of this field. Molecular genetics now presents an integral canon of biological knowledge which must be preserved and passed on to succeeding generations in academics... But its appeal as an arena for heroic strife against the Great Unknown is gone" (Stent 1970).

How wrong Stent was in this comment! Since then, concepts have constantly changed, and what was unbelievable only a couple of years ago, must be accepted now as facts.

One obvious detail that had to be ironed out was that of the organization of the genetic material in the nuclei of eucaryotes. Up to this time most of the understanding at the molecular level was accomplished through research in procaryotes. To be sure, much work has been done already before with eucaryotes, and these gave reasons to believe that, by and large, patterns established for procaryotes had enough generality to apply also to eucaryotes. Yet, there were ominous signs. To mention just two: the presence of highly heterogeneous huge RNA molecules (HnRNA) in the nuclei, though not in the cytoplasm of eucaryotes; and the posttranscriptional attachment of long poly-A (poly-adenylic acid) sequences at the 3′ (the "tail") end of mRNA in eucaryotic nuclei, before these left for the cytoplasm.

In my opinion, the turning point was when Britten and Kohne, in 1968, discovered that much of the DNA of eucaryotes was highly repetitive. As soon turned out, much of this DNA was not only highly repetitive, but also of very low

"complexity", i.e., of very low informational content. What was all this DNA doing in the nuclei? What is the meaning of a gene in these highly redundant sequences?

The bewildering gene

Some of the highly repetitive sequences in the DNA could be interpreted along the established concept of the gene, e.g., rRNA genes coding for the ribosomal RNA-components, were simply genes present in many copies. Yet, it would stretch the concept of the gene too much to call all the informationally dull, highly repetitive sequences of DNA by the name of "genes". Although it has been suggested that such repeptitive sequences fulfil "household functions", i.e., help maintain the organized structure of the chromosomes, it would seem that calling every stretch of DNA that fulfils some function as "gene" or "cistron", would make the terms vacuous.

The highly-repetitive sequences were just one class of repetitive sequences. There were also the intermediate- and the low-repetitive sequences, and these were dispersed in-between the classical cistrons. Models, like that of Britten and Davidson (1969) of regulatory sequences, were forwarded to maintain the image of discrete DNA sequences with specific function at specified sites along the chromosomes. But surprises came also from other sides: "insertion segments" (IS) with neither fixed sites nor constant numbers, were only the tip of the iceberg of the "transposons" which defied all the established concepts of genes. Yet, they had to be accepted as moving segments that mobilized even "ordinary" genes of the nuclei[3].

The finding of segments of the DNA that coded for two different polypeptides was in flat contradiction to the concept of the discrete material gene. Attempts to rationalize that these overlaps were special cases, resulting from selection pressure in the evolution of those viruses that had to maintain a capacity for a maximum number of functions in a minimum volume, failed. Soon it turned out that overlap in functions was not limited to viruses. For example, sequences at the "upstream" end of structural genes, had often double functions, such as being both attachment sites for the regulating molecules and coding sequences for the polypeptide products. Towards the end of the 1970s, even the "structural gene" could not be maintained any more as a continuous sequence of DNA, when it was found that many and quite extensive segments, the "introns", had to be extirpated before translation.

The "Scientific American" is a science journal for non-specialists. It cannot trust its readers to have learned in advance the words in their social context. Neither can it trust experts to agree with other experts on the meaning of terms. Thus, it must explicate what is meant by a sentence like: "The gene that encodes the products". Here is an experiment in definition:

> "The string of triplets constituting a gene are flanked by long non-coding spacers and signaling regions that are not transcribed into RNA and by other stretches that are transcribed into messenger RNA but are not translated; the genes themselves are often split into pieces by noncoding intervening sequences ('introns')" (Grivell 1983).

This is a heroic effort to maintain the "gene" concept more or less in the sense of the "cistron" of Benzer—a stretch of DNA encoding for a product—and allow all the late discoveries of molecular biology to "flank" it, as instrumental qualifications: flanked by signaling regions; flanked by non-coding regions; flanked by stretches that are transcribed into mRNA but not translated; split into non-coding intervening sequences.

Dawkins may still talk of "The Selfish Gene" as the discrete material entity as Muller would have done 50 years ago:

> "A particularly remarkable molecule was formed... Replicator ... it had the the extraordinary property of being able to create copies of itself... They have come a long way, these replicators. Now they go by the name of gene, and we are their survival machines" (Dawkins 1976).

But while this concept may perhaps be useful at the level of population genetics or evolution, it can hardly be applicable to the molecular biologist.

This is not the place to summarize the explosive developments in the experimental research of the structural and functional organization of the genetic material. However, a casual glance at the current genetic literature would be enough to reveal that although the term "gene" is very much in use, it means different things for different people. Some would reserve the term strictly for the structural sequences (introns included?). Others would prefer to call the whole sequence, related to a given polypeptide, all the various structural and regulating functions included, by the name "gene". Even those who isolate "discrete genes" and engineer them are aware that it makes a lot of difference what they take to be their unit of reference.

Today the gene is not just the material unit, or the instrumental unit of inheritance, but rather a unit, a segment that corresponds to a unit-function, as defined by the individual experimentalist's needs. It is neither discrete—there are overlapping genes; nor continuous—there are introns within coding sequences; nor does it have a constant location—there are transposons; nor a clearcut function—there are pseudogenes; not even constant sequences—there are "consensus" sequences; or definite borderlines—there are variable sequences both "upstream" and "downstream".

However it is still an extremely helpful concept because with each new bewildering experimental observation geneticists realized more the provisional aspect of their constructs and unconsciously attached less meaning to the "added value" of their abstractions, turning perhaps for the first time the concept really into that of an intervening variable. Such a variable is "simply a quantity obtained by a specified manipulation of the values of empirical variables" (MacCorquodale and Meehl 1948). Nothing less and nothing more!

When Elkana (1974) talks of the development of the concept of energy, he finds it irresistible to repeatedly quote a motto by H. A. Kramers:

3 On December 10, 1983, the Nobel Prize for medicine and physiology was awarded to Barbara McClintock for her discovery of unstable "jumping genes" in maize in the late 1940s. Although her work has been well known and respected all these years, it was ignored as not being a substantial contribution to our genetic body of knowledge. It took nearly 40 years for the genetic community to accept McClintock's concept of the gene. I wish to suggest that refusing to assimilate McClintock's concepts at the late 1940s and the 1950s was an act of self-defense of the genetic community. At the time when the material basis of the genetic entities was finally established as specific and discrete sequences of DNA, with well defined modes of function, her concept of genes that were unstable both in their location and in their function, was too disruptive to accept. Only now, at the age of anarchy in the formulation of genetic entities, could McClintock's heterodox genes be enthusiastically admitted into our expanding zoo of notations for genetic units

> "My own pet notion is that in the world of human thought generally, and in physical sciences particularly, the most fruitful concepts are those to which it is impossible to attach a well defined meaning".

This could also be quoted in reference to the concept of the "gene" and it would highlight its extraordinary success. As noted all this was achieved by and large without falling into the "fallacy of misplaced concreteness", though misunderstanding and misconceptions sometimes do arise. Here is an example:

> "S. L. Washburn's (May 1978) article contains a glaring error that psychologists have begun to accept. Washburn asks, 'How many shared genes are there within a species such as *Homo sapiens?*' ... He interprets King and Wilson's article to say that humans and chimpanzees 'share 99% of their genetic material' and concludes from this that humans, therefore, 'share in fact, more than 99% of their genes' ... However, a more useful way of looking at it is to say that, of the eight proteins, two showed a genetic difference. Thus, those same data can be used to suggest that the genetic difference between humans and chimps is substantial: one quarter of the proteins were genetically different.
>
> In other words, even though DNA is very similar, the proteins are very different" (Plomin and Kuse 1979).

Although it is still true that humans and chimpanzees have extremely similar proteins, even if in one of four there is a diagnostic single amino acid substitute, it is fortunate for the dignity of man that there is more to the gene than just a sequence of polypeptide coding nucleotides. This misunderstanding, however, highlights the risks that we may run when every group of investigators circumscribes its own gene.

> "'When I use a word,' Humpty Dumpty said, 'it means just what I choose it to mean—neither more nor less.' 'The question is,' said Alice, 'whether you can make words mean so many different things.' 'The question is,' said Humpty Dumpty, 'which is to be master—that's all.' Alice was too much puzzled to say anything..." (Through the Looking Glass)

Let us pause for a moment, so that we shall not be too much puzzled to say anything.

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