

WHAT IS "HETEROSIS"?¹

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IT IS not my purpose in this paper to present or to discuss the actual basic causes or the fundamental mechanisms which bring about the increased size, the excessive kinetic energy, the increased productiveness, resistance to disease or to unfavorable conditions of the environment, the "stimulating effects of hybridity," the so-called "hybrid vigor" of English writers and "Luxurieren" of many German writers, which may be observed in this or that cross-bred organism when compared with corresponding inbred or relatively more pure-bred organisms.

My object is merely to consider the spirit and the coverage of the word "heterosis" which I proposed in 1914 to replace the more cumbersome word "heterozygosis" which had been found useful by a few geneticists of that time, myself among them.

What I have to say about the meaning of the word "heterosis" will be better understood if it be kept in mind that I was, as far as I know, the first English-language geneticist to adopt and promote the use of the brilliantly conceived terminological proposals of the Danish plant physiologist, DOCTOR W. JOHANNSEN, which have contributed so much to the precision, clarity and stability of modern genetical terminology. JOHANNSEN'S proposals of "phenotype," "biotype," "gene," "genotype," etc., were launched in 1909 in his "Elemente der exakten Erblchkeitslehre," and in that same year his word "biotype" appeared in the title of one of my Carnegie Institution publications, "*Bursa bursa-pastoris* and *Bursa Heegeri*; biotypes and hybrids."

In proposing the German word "Gen," for whose English form "gene" I was more or less responsible, JOHANNSEN pointed out that DARWIN'S word pangene which had come into use as a specific improvement over the older, ambiguous term "Anlage," was a double expression, consisting of the two parts, "pan" and "gene" of which the first syllable, "pan," was wholly immaterial and irrelevant, and only the second syllable represented the concept which it was desired to express. The word "pangene" had the further disadvantage that it was closely identified with DARWIN'S "provisional hypothesis" with its migrating gemmules and their differential assortment during ontogenetic development. By omitting the non-essential half of the word "pangene," JOHANNSEN arrived at his neat word "Gen" which was thus freed from the Darwinian proposals, and he added the specific stipulation that "das Wort 'Gen' ist völlig

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frei von jeder Hypothese"—"the word 'gene' is completely free from every hypothesis!"

It was this completely non-committal quality of JOHANNSEN'S proposed terms that impressed me, since they harmonized with the complete open-mindedness that I have always considered essential in scientific research.

The proposal to use "heterosis" instead of "heterozygosis" can be explained in a manner closely paralleling the statements of JOHANNSEN in launching the word "gene," as quoted above, for the word heterozygosis like the word pan-gene is a double construction of which the first half represents the important significant concept. The words "homozygous" and "heterozygous" were already in general use in reference to Mendelian paired genes, so that the "zygosis" part of the word "heterozygosis" seemed to connote that the effective differences which resulted in the increased size, speed of development, etc., in cross-bred organisms were solely due to heterozygous Mendelian genes, a view that I desired to avoid, even though I proceeded to discuss the problem on the basis of the known distribution of Mendelian genes. The word "heterosis" was chosen in the same spirit as JOHANNSEN'S word "gene," namely that it should be *free from every hypothesis*. It represented a group of observable phenomena for which any subsequent student was free to propose his own explanation without thereby being obliged to abandon the word "heterosis."

DOCTOR EAST and I used the word "stimulation" and many others used the expression "hybrid vigor" in discussing these phenomena, but both "stimulation" and "vigor" are ambiguous terms and refer solely to the fact that there is *increased* size or other valuable qualities in the cross-bred as compared with the pure biotypes or the different species or different varieties whose union produced the cross-bred in question. The existence of "stimulation" or "increased vigor" is discovered only when it is translated into visible observable phenomena. Any attempt to distinguish between the visible and the invisible phases of the effects of differences in uniting gametes does not appear to be practically justifiable, and it was intended that the word heterosis should include the entire process from start to finish.

In proof of this intended coverage I will quote from my invitation lecture delivered at Göttingen, Germany, in mid-July, 1914, in which the word "heterosis" was first proposed, and from a paper written at the same period, on "Duplicate genes for capsule form in *Bursa bursa-pastoris*," through which latter medium the word "heterosis" came to the attention of other geneticists; the Göttingen lecture was delivered less than three weeks before the outbreak of World War I, and its publication was delayed for eight years, finally appearing in print in 1922.

I quote verbatim, but in considerably contracted form, from my paper on duplicate genes (1914, pp. 126, 127): "My investigations on the effect of cross and self-fertilization in maize had led me as early as 1907 to the conclusion that . . . hybridity itself,—the union of unlike elements, the state of being heterozygous—has . . . a stimulating effect upon the physiological activities of the organism, which effect disappears as rapidly as continuous breeding

reduces the progenies to homozygous types. . . . There is some danger of misconception due to the fact that all discussion of the stimulus of hybridity have taken as their starting point, for the sake of simplicity, the typical Mendelian distribution of the germinal substances. The essential features of the hypothesis may be stated in more general terms, as follows: The physiological vigor of an organism as manifested in its rapidity of growth, its height and general robustness, is positively correlated with the degree of dissimilarity in the gametes by whose union the organism was formed. . . . The more numerous the differences between the uniting gametes—at least within certain limits—the greater on the whole is the amount of stimulation. . . . These differences need not be Mendelian in their inheritance. . . . To avoid the implication that all the genotypic differences which stimulate cell-division, growth and other physiological activities of an organism are Mendelian in their inheritance and also to gain brevity of expression I suggest that . . . the word 'heterosis' be adopted."

From the Göttingen lecture I make only the following brief quotation: "Bei der Frage die uns heute beschäftigt, halte ich es für unbedingt notwendig, scharf zwischen den Tatsachen und der daraus abgeleiteten Theorie zu unterscheiden. Mit den empirischen Tatsachen wird man immer zu rechnen haben, während sich die Theorie vielleicht als unzulänglich erweisen wird. Es ist sehr möglich, dass noch andere Gründe für die Heterosis und Inzuchterscheinungen gefunden werden." Translated this says that "I hold it to be absolutely necessary to distinguish sharply between the facts and the theory derived from them. We must always reckon with the empirical facts, while the theory may prove itself to be inadequate. It is very possible that still other bases may be found for the heterosis and inbreeding phenomena."

Other relevant statements could be quoted from this lecture, but since their meaning is in close agreement with the statements above quoted from the paper on duplicate genes it does not appear necessary to repeat them here. These quotations leave no doubt that I offered the word "heterosis" to cover the real, observable phenomena and that it was definitely intended to include cases in which the effective differences between uniting gametes might be due to anything else than Mendelian genes, as well as the differences caused by such Mendelian genes, if the latter were not individually analyzable as Mendelian genes. I have not the least doubt that if I had known at that time the striking phenomena which our brilliant colleague, DOCTOR B. O. DODGE, has discovered in *Neurospora*, and has discussed under the expression "heterocaryotic vigor," I would have enthusiastically presented them as an example of heterosis which was associated with a mechanism clearly different from that which produced the typical Mendelian distribution of paired genes. In *Neurospora* the heterosis is evidently the result of the coexistence and interactions of two unlike whole nuclei operating in a common cytoplasmic mass. I can see no reason to assume that the fundamental nature of the phenomena here manifested is different from the increased activity which results when two unlike nuclei fuse and rearrange their unlike elements in the organization of a single

nucleus. In either case the result is assumed to be due to the fact that elements of unlike constitution are brought into sufficiently close association that effective interactions can and do take place.

That my Göttingen lecture was from the time of its publication understood by competent biologists exactly as here stated, can be substantiated by reference to the abstracts published in "Botanical Abstracts" and in "Botanisches Centralblatt," immediately after the printing of this lecture. In "Botanical Abstracts" DR. D. F. JONES says: "The increase in size and vigor resulting from crossing is called heterosis." and in "Botanisches Centralblatt," DR. ELISABETH SCHIEMANN states: "Der Verf. nimmt an, dass bei heterozygoter Konstitution das Protoplasma grössere Fähigkeit besitzt, und bezeichnet die durch diese erhöhte physiologische Fähigkeit bedingte grössere Wüchsigkeit und Ertragsfähigkeit als Heterosis."

A review of other relevant literature since that time shows a general agreement with the author as to what is to be understood by the word "heterosis," and the word is correctly defined in the MERRIAM-WEBSTER *New International Dictionary*, Second Edition. It defines "heterosis" as "The greater vigor or capacity for growth frequently displayed by crossbred animals or plants as compared with those resulting from inbreeding." This same great standard dictionary defines "Hybrid vigor" as "Vigor resulting from hybridity. specif. heterosis."

This synonymy between "heterosis" and "hybrid vigor" is obvious in those cases in which the expression "hybrid vigor" can be appropriately used, and this was clearly recognized and strongly supported by EAST and JONES, the two geneticists of that time who can be recognized as best equipped to speak authoritatively and critically on the meaning of these terms. In their admirable book (1919) on "Inbreeding and outbreeding: their genetic and sociological significance," Chapter VII carries the caption "Hybrid vigor or heterosis," and the context shows decisively that the "or" of the heading signified the synonymy of these terms, not an antithesis between them. In the writings of most other authors the same synonymy has been in evidence, and only rarely has an expression slipped in, which implied that an author considered heterosis to be something more fundamental than hybrid vigor. It seems unfortunate in this connection that W. GORDON WHALEY (1944) should state in "Botanical Review" in his otherwise admirable compilation and discussion of heterosis, that "rather erroneously this term 'heterosis' has become established in the literature as a synonym for hybrid vigor. By the original definition 'heterosis' refers to the developmental stimulation resulting by whatever mechanism, from the union of different gametes. 'Hybrid vigor' denotes the manifest effects of heterosis." I hope I have in the foregoing quotations completely refuted this interpretation of what was involved in "the original definition."

It may be noted that I never used the words "hybrid vigor" in the presentation of my researches in which heterosis was involved. My preference for "heterosis" to its synonym "hybrid vigor" may be explained by the fact that my unexpected discovery and demonstration of this phenomenon were made within the genetical materials included in a small population of white dent

maize which was initially assumed to be genotypically uniform. All of my inbred lines were started from plants in this original population whose sole recognized differences consisted in the possession of different numbers of rows of grains on the female spikes or ears. Although I referred to the crossing in this material as hybridization in accord with general modern genetical usage, there was great contrast between these crosses of biotypes derived from a uniform strain of the single species *Zea mays* L. and the older species hybrids in which hybrid vigor had been frequently so strikingly presented. For this reason it seemed more appropriate in this case to speak of heterosis than of hybrid vigor. This may indicate that "heterosis" has a slightly more extensive coverage than "hybrid vigor," that is, that while all hybrid vigor is heterosis, not all heterosis can be with equal propriety termed "hybrid vigor." This is particularly the case in *Neurospora* and other groups of Fungi in which the juxtaposition of unlike elements is brought about by nuclear migrations, not by cross-fertilization.

Limitations of time do not permit me to essay an adequate consideration of the effective causes of heterosis, but I am impelled by the opportunity this occasion offers, to make several statements on this phase of the subject. I hold that heterosis is not a unitary phenomenon, but a complex series of phenomena for which no single cause or mechanism can be properly assumed to apply to all cases. The early hypothesis of DOCTOR EAST and myself that heterogeneity of the protoplasmic materials results in greater physiological effectiveness need not be discarded because of any seeming plausibility of DOCTOR JONES's hypothesis (1917) that many linked size factors are dominant in character, and that increased vigor may be produced by the increased number of such dominant favorable factors which will be present when paired chromosomes are of unlike constitution, as they are likely to be when they have come from unlike parents, than when they are derived from like parents.

In relation to JONES's hypothesis, it is important to keep in mind that the phenomenon of dominance in size factors is a demonstrable reality only when there is a single gene whose presence results in a relatively considerable change in size, as in MENDEL's cross between tall and dwarf peas and in many other examples of hereditary dwarfism found by other investigators in both plants and animals.

When NILSSON-EHLE (1909), followed closely by EAST (1910), discovered the first examples of duplicate genes, and therefrom developed a Mendelian interpretation of quantitative-factor inheritance, it was assumed by EAST and accepted by most other geneticists as a necessary condition for such interpretation, that we pre-suppose the absence of dominance in the genes producing the quantitative characters. In an important paper that has been long since overlooked and apparently completely forgotten, I showed, more than 27 years ago (SHULL 1921), that we need not deny the occurrence of dominance of size factors in the Mendelian interpretation of quantitative inheritance. The small effects produced by any individual size modifying "quantitative" gene compared with the fluctuations produced by environmental and developmental variations, make the question whether any such gene produces as great

effect in the heterozygous phase as in either homozygous phase wholly academic, since it can never be settled; the correct scientific attitude in such a situation is one of skepticism, when any one asserts either that such quantitative paired genes are *generally* dominant and recessive, respectively, or that they *generally* have an intermediate effect in the heterozygous phase as compared with the two alternative homozygous phases.

In view of the complete absence of the conditions necessary for a determination of the occurrence of dominance versus intermediacy of size factors in their heterozygous phase it is regrettable that one can read in certain recent papers of RICHEY (1945) and others that the cumulative effects of dominant favorable genes is "the generally accepted" explanation of hybrid vigor. Such a statement seems to imply that the heterosis problem has been completely solved and requires no further investigation. To point the fallacy of such a conclusion I call attention to an important paper by EAST, published in 1936 only two years before his untimely death. DOCTOR EAST was the greatest authority on the subject of heterosis, and his paper under the simple title "Heterosis" is the best and most comprehensive treatment of the subject now available. In this paper EAST considered and specifically rejected the hypothesis that dominant favorable factors play any role in heterosis. He offered a new suggestion based, like JONES's hypothesis, on the linkage of quantitative genes, but proposing the hypothesis that heterosis is due to partially additive effects of multiple alleles. JONES himself (1945) has recently demonstrated that apparently degenerative changes in six mutations in homozygous inbred lines of maize have produced notable degrees of heterosis when these new mutant forms are crossed back to the inbred parent strains. These results seem to be in essential agreement with the later hypothesis of EAST, above mentioned. They do not support JONES's reiteration that "heterosis is interpreted as an accumulative effect of favorable heredity from both parents." Instead of the heterosis being due in these cases to the accumulation of favorable dominants, they are clearly due to the occurrence of *unfavorable recessives*. CASTLE (1946) offers a new and somewhat different explanation of the heterosis which JONES has demonstrated in his six new "degenerate" mutants from inbred strains. CASTLE points an analogy to the "killer gene" found by SONNEBORN in *Paramecium*, and suggests that the heterosis is due to the (anaphylaxis-like) sensitization of the new recessive "degenerate" genes by the parental dominant gene at the same locus.

The several hypotheses which have been proposed for the explanation of heterosis are in the main not mutually exclusive: (a) the entrance of a sperm into a "foreign" cytoplasmic environment may in some cases produce an initial favorable reaction which may manifest itself in the F_1 and not be repeated or not repeated in the same degree in F_2 and subsequent generations (A. F. SHULL 1912); (b) protoplasmic heterogeneity may favor increased metabolic activity (E. M. EAST and G. H. SHULL); (c) linked dominant favorable factors may confer some advantages in heterozygotes as compared with homozygotes (D. F. JONES, F. D. RICHEY, and others); (d) Multiple alleles produced by repeated mutations at single loci may produce additive effects when unlike

alleles are present (E. M. EAST); (e) JONES'S (1946) demonstration that striking heterosis resulted from back-crossing of several mutant strains to the parental homozygous inbred strain, gives still another mechanism for the production of heterosis, for here it is not the accumulation of favorable dominants, but the rare occurrence of an unfavorable recessive that induces heterosis; and (f) for this case CASTLE (1946) proposes a sensitization of the non-mutated parent gene by its mutated allele, or *vice versa*, of the nature of an anaphylaxis, that produces the heterotic effect. Since these mechanisms are not mutually exclusive two or more of them may be jointly involved in any single example of heterosis.

Any attempt to restrict "heterosis" to any one of these possible causes of increased vigor in cross-bred organisms, would render the term heterosis relatively useless and that would be a distinct misfortune for the cause of stability in genetic terminology. As an example of such restriction I quote from DR. PAULA HERTWIG (1936, p. 49, 50): "Dass gerade bei Artbastarden von Säugertieren besonders kräftige F₁-Tiere häufig sind, lässt darauf schliessen, dass wir es hier kaum mit Heterosis im eigentlichen Sinne zu tun haben. Das stärkere Wachstum wird wohl weniger darauf zurückzuführen sein, dass eine grössere Heterozygotie und Anhäufung von dominanten Faktoren erreicht worden ist, es scheint mir vielmehr wahrscheinlicher, dass es sich um die Wirkung einiger weniger komplementärer Faktoren handelt, die auf das inkretorische System einwirken und dadurch wachstumsfördernd sind." If DOCTOR HERTWIG is correct that complementary genes are producing a favorable growth-enhancing modification of the secretory system, I interpret that as merely recognizing such complementary factors as a part of the heterotic mechanism, not as justification for the suggestion that no heterosis is involved.

A similar statement can be made regarding the recent observation by ROBINS and students, that specific growth promoting substances occur in the excised roots of heterozygotes that are not present in either of the homozygous parents.

The fundamental consideration for the objectives of the present paper is that, although five or six sources of heterosis have been proposed and discussed by different authors, and others may be offered in the future which have not yet been dreamed of, the non-committal quality of the word allows authors to continue to use the word "heterosis". If the spirit in which the word was proposed is maintained, as urged in this paper, heterosis will always continue to be a useful genetical term, and new researches will be encouraged to determine the factors involved in each specific example.

POSTSCRIPT

Since this address was written and delivered, my attention has been drawn to a misuse of the word heterosis, which I consider unfortunate and unnecessary, and which I hope will be discontinued. This is the use of the expression "negative heterosis" for a situation which has no apparent or obvious relationship with the phenomena for which the word "heterosis" was proposed and has been generally adopted. I can find no more justification for the expression

"negative heterosis," than there would be for calling hydrophily "negative xerophily," or photosynthesis "negative respiration."

By definition, heterosis is the *increase* of size, yield, vigor, etc. If there is no such *increase*, there is no heterosis. A decrease in size, vigor, etc., should be treated as another phenomenon, since it is not clear that any of the causes involved are the same as those which produce an increase of these functions.

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