Letter to the Editor

Parasitic Epistasis

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As early as 1907, Bateson (2) observed modifications of the classical dihybrid 9:3:3:1 ratio to various ratios such as 9:7, 15:1, 9:3:4, or 12:3:1, etc. due to *gene interaction.* The phenomenon was named "epistasis" and is defined as "a form of gene interaction whereby one gene interferes with the phenotypic expression of another nonallelic gene (or genes), so that the phenotype is determined effectively by the former and not by the latter when both genes occur together in the genotype" (4). The gene that alters the expression of another is known as the "epistatic" gene and the one whose expression is altered is known as the "hypostatic" gene. Epistatic genes may be effective in homozygous dominant (dominant epistasis), recessive (recessive epistasis), or heterozygous forms. In single-locus dominant epistasis, the dominant allele at the A locus suppresses the expression of both the dominant and the recessive alleles at the B locus, and as a result the 9:3:3:1 ratio becomes 12:3:1. In two-locus reciprocal dominant epistasis (ie, A epistatic to B, b, and B epistatic to A, a) the dihybrid ratio becomes 15:1. Similarly, in the case of single-locus recessive epistasis, the recessive allele at one locus suppresses both the dominant and the recessive alleles at the other locus, resulting in a 9:3:4 ratio. In two-locus reciprocal recessive epistasis, the dihybrid ratio becomes 9:7. These epistatic ratios are normally observed in the segregations of morphological characters that are under the control of structural genes.

Epistatic ratios for plant disease resistance also have been reported in the literature, and the disease resistance ratios have usually been ascribed to resistance gene interaction. However, as explained in this report, such epistatic ratios also can result from interaction between two parasites simultaneously present on each member of the segregating host population.

Interactions among different true and incidental parasites are quite common in nature. A single host plant may be viewed as a miniature ecological system on which various parasites interact and survive by forming a disease complex. In a disease complex, one parasite may induce resistance or susceptibility, or may remain neutral to another parasite. The inducer may be termed the epistatic parasite and the one against which the modification is induced, the hypostatic parasite. The phenomena is hereby termed "parasitic epistasis." The origin of certain epistatic ratios due to parasitic epistasis is discussed below.

Parasitic epistasis in dihybrid progeny. Suppose that the dominant allele R_1 imparts resistance to parasite A while its recessive allele r_1 results in susceptibility. Similarly, assume that dominant allele R_2 provides resistance to parasite B and its recessive allele r_2 imparts susceptibility. The dihybrid cross of $R_1R_1r_2r_2 \times r_1r_1R_2R_2$ should yield an F_1 that is resistant to both parasites, and the F_2 from this cross should segregate as follows:

9 R_1-R_2- resistant to both A and B parasites,
3 R_1-r_2r_2 resistant to A but susceptible to B,
3 $r_1r_1R_2$- susceptible to A but resistant to B,
1 $r_1r_1r_2r_2$ susceptible to both A and B parasites.

This classical dihybrid ratio would be altered if, for example, parasite A, which is avirulent on plants of R_1-r_2r_2 genotype, somehow altered the plants in such a way that they became resistant also to parasite B (induced resistance). Double inoculations of a segregating F_2 population with parasites A and B would then yield an epistatic ratio, 12 resistant to both parasites : 3 resistant to B only : 1 susceptible to both A and B parasites. The doubly inoculated population would segregate 3R:1S with respect to parasite A, but 15R:1S for parasite B. The 15:1 ratio is characteristic of duplicate genes; emergence of this ratio would be misleading in parasitic systems. Such a situation was originally described in an interaction of tomato and *Verticillium* + *Fusarium* (7).

On the other hand, parasite B to which R_1-r_2r_2 plants are ordinarily susceptible, might conceivably alter the R_1-r_2r_2 host phenotype in such a way that susceptibility to parasite A also would occur. In such a situation, double inoculations of an F_2 population would result in the epistatic ratio, 9 resistant to both A and B : 3 resistant to B only : 4 susceptible to both parasites. Segregations for reaction to parasite B in this population would be 3R:1S, but for parasite A the epistatic ratio 9R:7S would result. This ratio, ordinarily associated with complementary genes, would be misleading in systems involving two parasites. A case of this type was found in an interaction of tomato and root-knot nematode + *Fusarium* (5).

Parasitic epistasis and polygenic inheritance. When an F_2 host population segregating for resistance versus susceptibility is appropriately tested against relatively pure culture(s) of the pathogen(s), an oligogenic or epistatic ratio for resistance may occur (6). However, when tested against impure cultures or a mixture of pure cultures, the segregations may show continuous distribution of reaction types suggesting polygenic resistance. Numerous studies show that different parasite races or species interact and modify disease responses when present together on the same host. Therefore, so-called polygenic segregations may be an artifact of parasitic epistasis. Two examples will clarify my point.

Resistance to Fusarium wilt in certain tomato cultivars was thought to be polygenic until natural infection by root-knot nematodes was minimized. When the nematodes were controlled, the resistance appeared to be monogenic. When various tomato cultivars resistant to Fusarium wilt were artificially inoculated with root-knot nematode, the resistance again appeared to be polygenically inherited (8).

In another case, Smith and Dick (9) tested resistance to Fusarium wilt in cotton under field conditions. The resistance showed a polygenic mode of inheritance, but when the segregating progeny were retested in the same field after it had been treated with the nematicide, ethylene dibromide, resistance to Fusarium wilt segregated in a monogenic ratio. I believe that polygenic resistance may, in fact, often be a modified oligogenic resistance, particularly if the experiments are conducted under uncontrolled experimental conditions. Ellingboe's (3) assertion that horizontal resistance is an artifact of experimental procedures seems valid.

Theoretically, the distribution of reaction types in an F_2 host population segregating for a pair of alleles at each of two resistance genes showing equal and additive effects without dominance might also indicate polygenic inheritance when challenged by a mixture of parasites. Suppose that an F_2 host population is exposed to a mixed inoculum of four interacting parasite races, two each of the two different parasites A and B. Assume that there are two alleles R_1 and r_1 at resistance locus R_1 effective against races A_1 and a_1 of

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parasite A, and two alleles R_2 and r_2 at the second locus R_2 effective against races B_1 and b_1 of parasite B. Alleles R_1 and R_2 show resistance and r_1 and r_2 show susceptibility to the respective parasite races, but there is no dominance. An increase in level of resistance by R_1 and/or R_2 is proportional to the increase in level of susceptibility by r_1 and/or r_2. All four races, present in equal proportions, interact intra- and interspecifically on all host genotypes and thus individually add or subtract a certain level of disease expression. Interactions between 16 host genotypes and 16 combinations of four races will give rise to a matrix of disease expressions which can be classified in continuous phenotypic classes. There are nine host genotypes distributed into five phenotypic classes corresponding to 0, 1, 2, 3, and 4 host alleles. Five phenotypic classes represent five different levels of disease produced by specific interactions among parasite races and host alleles. The frequency of these five different levels of disease is described by the histogram in Fig. 1. A given level of disease is ascertained by the number of plus (+) and minus (−) signs in the matrix. As pointed out earlier, a plus (+) interaction adds and a minus (−) interaction subtracts an equal increment of disease from the total expression of the phenotype. For example, on $R_1R_1R_2R_2$ the four corresponding races $A_1A_1B_1B_1$ act in the same direction, each subtracting an increment of disease, which thus exceeds the midrange by 4(−). On $r_1r_1r_2r_2$ the four races $a_1a_1b_1b_1$ also act additively, each adding an increment of disease, thereby exceeding the midrange by 4(+). On $R_1R_1R_2r_2$ or $R_1r_1R_2R_2$ two races add, and two cancel one another's contribution to disease expression and thus add nothing. These interactions, therefore, give rise to disease expression that exceeds the midrange by 2(−). Similarly $r_1r_1R_2r_2$ and $R_1r_1r_2r_2$ give rise to disease expression that exceeds the midrange by 2(+). The interactions among four races and double heterozygotes give zero disease expression, ie, the midrange disease-phenotype. Midrange phenotype occurs due to inter- and intraspecific interactions among four races of the two parasite species. For example, on double heterozygotes $R_1r_1R_2r_2$ the corresponding races show intraspecific (ie, $A_1 \leftrightarrow a_1$ and $B_1 \leftrightarrow b_1$) interaction and balance one another out, and on double homozygotes $R_1R_1r_2r_2$ and $r_1r_1R_2R_2$, the races interact interspecifically (ie, $A_1 \leftrightarrow b_1$ and $a_1 \leftrightarrow B_1$) to cancel each other's contribution to the disease-phenotype. The entire phenotypic pattern shows a normal distribution indicating a polygenic inheritance. This disease pattern will generally remain unchanged even if the specific interaction takes place among four races of the same parasite or four different parasites infecting the same tissue of the plant, eg, vascular diseases. As the number of resistance genes and corresponding parasite races increase, the normal curve will tend to become smoother. For example, with three resistance genes seven phenotypic classes in disease expression will appear, and with four genes the number of such classes will rise to nine and with n genes to $2n + 1$ classes.

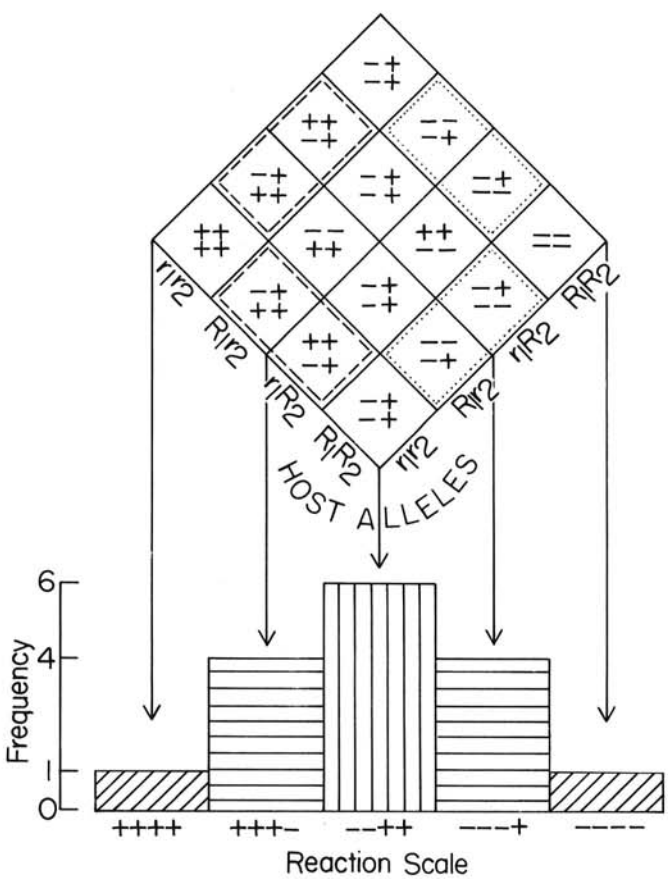

Fig. 1. Polygenic type of disease segregation in an F_2 host population due to parasitic epistasis. The pair of alleles R_1-r_1 and R_2-r_2 at two resistance loci R_1 and R_2 are of equal and additive effect without dominance. The disease-phenotype is proportional to the number of plus (+) and minus (−) disease increments that are mediated by various combinations of four parasite races A_1, a_1 and B_1, b_1. Races A_1, a_1 correspond to alleles R_1, r_1; races B_1, b_1 correspond to alleles R_2, r_2, respectively. Minus (−) and plus (+) indicate increase and decrease in an increment of disease, respectively.

Mechanism of parasitic epistasis. The degree to which an F_2 distribution reflects the underlying genetic component depends upon heritability and environmental variables. Heritability and environmental variables have special significance in parasitic systems. Unlike most genes, the heritability of resistance genes is controlled by two different environments: an internal environment provided by the parasite(s), and an external physical environment. Either one or both of these environments can influence the heritability of the resistance genes. Here we are only concerned with the influence of the internal host environment. A simple environment such as provided by the presence of a single parasite race or species allows high heritability. High heritability results in discontinuous variability, the kind shown by Mendelian segregations. The internal environment becomes complex as the number of parasitic races or species increase in or on the host. An increase in variability of internal environment, caused by interactions among many parasites, may result in low heritability. Low heritability gives normal distribution, the kind shown by polygenes. If the environment is complex and heritability is low, normal distribution of reaction types may be observed even if the resistance is controlled by a single locus (1).

Parasitic epistasis most probably operates through physiological changes induced by the interacting parasites in or on the host. All physiological modifications are ultimately controlled by the genetic systems of the host and of the parasite(s). Therefore, parasitic epistasis has a genetic basis.

Influence of parasitic epistasis on breeding for resistance. It is obvious that if the resistance ratio is not truly Mendelian, the number of identified genes will be misleading. Suppose a plant breeder discovered a complementary ratio for resistance which, in fact, appeared as a result of parasitic epistasis. Now if a cultivar possessing such pseudogenes was given to another breeder to transfer these two genes into a new cultivar, his efforts will fail. Such a pursuit will not only cost money and time but will also muddle the scientific literature.

It is important to identify genes for resistance and virulence in order to obtain effective disease control through deployment of genes in space and time, and for synthesis of multigene or multiline cultivars. Therefore, testing of segregating host populations for resistance against a target parasite needs to be done under relatively controlled environmental conditions, such as those provided by greenhouse or even isolated field plots, by using homogeneous (pure) cultures of the pathogen. In the case of soilborne pathogens, fumigated soil should be used to study inheritance of resistance. However, from a practical standpoint, when overall resistance to various pathogens is sought and where understanding of underlying genetic mechanism(s) is not important, field testing of segregating host populations against parasite(s) may suffice. But field evaluations may not be useful in long-term disease control, especially where high levels of resistance is required.

Validity of phenomenon of parasitic epistasis. Currently in the literature there are ~96 reports of epistatic ratios for resistance

TABLE 1. A summary of numbers of published papers on host resistance showing modified genetic (epistatic) ratios

Type of disease	Mode of parasitism	Papers (no.) showing epistatic ratios: 9:7	15:1	13:3	Papers reviewed
Rusts	obligate	35	11	2	401
Smuts	obligate	3	1	0	170
Mildews	obligate	5	2	0	169
Wilts, scabs, rots	facultative	17	3	2	292
Viruses	obligate	6	2	0	102
Nematodes	obligate	2	0	0	149
Nonfungal diseases		6	1	0	100
Totals		74	18	4	1,383

(Table 1). I argued the occurrence of such ratios in an earlier paper (6). Some of the reports indicating epistatic ratios were subsequently shown to be incorrect. It is likely that other reports showing epistatic ratios for disease resistance may also be incorrect and this should be investigated further. I believe that non-Mendelian segregations for resistance or virulence, particularly in man-manipulated systems, are unlikely to occur because of the conditional evolution of host-parasite genes. When non-Mendelian ratios are found, the possible role of parasitic epistasis should be investigated.

The literature indicates that epistatic ratios are more commonly found for resistance to obligate rather than facultative parasites, and that polygenic inheritance is more common for resistance to facultative rather than obligate parasites (Table 1). The presence of physiologic specialization in obligate parasites and its absence in facultative parasites may contribute to the nature of parasitic epistasis. Moreover, whether the parasites are airborne or soilborne would also influence the expression of parasitic epistasis. Interactions among airborne parasites are less complex than those of soilborne parasites. That may be why epistatic ratios are often obtained from the interaction of airborne obligate parasites and a polygenic mode of inheritance from the interaction of soilborne, facultative parasites. In both cases, the host reaction portrays a modified response to the target parasite due to parasitic epistasis and thus is pseudogenetic in nature.

All the reports showing epistatic ratios or polygenic inheritance may not be due to parasitic epistasis (Table 1). Carefully controlled experiments conducted under growth chamber or greenhouse conditions may reveal true genetic epistasis and polygenic segregations, particularly, where reactions of an F_2 host progeny are studied against a single pathogen isolate or a single race. However, most of the papers included in Table 1 contain results from field conditions in which the likelihood of infection caused solely by the target parasite is reduced.

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