CURRENT STATUS OF THE GENE-FOR-GENE CONCEPT

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INTRODUCTION

One of the most successful means of controlling plant diseases has been the development of varieties with major or vertical resistance genes. This type of resistance is easily manipulated in a breeding program and is effective until strains of the pathogen to which it does not confer resistance become established. Then, if another gene that conditions resistance to the new strains of the pathogen is available, this resistance gene may be incorporated into the variety by the plant breeder. In doing this, the breeder either consciously or unconsciously is applying the principle of the gene-for-gene hypothesis. Plants resistant to races that are virulent on old varieties possess the new resistance gene. With the diseases of some crops, this process has been repeated at relatively frequent intervals (40, 42, 82). However, in some instances a single gene has conferred adequate resistance for many years (80, 82).

In plant diseases caused by living organisms, the same phenomena: infection type in rusts, percent of infected plants in smuts of cereals, fleck or lesion in apple scab, are criteria of both the reaction of the host and the pathogenicity of the parasite. They indicate the relative resistance or susceptibility of the host and the relative avirulence or virulence of the parasite.

The gene-for-gene hypothesis was proposed (20, 25) as the simplest explanation of the results of studies on the inheritance of pathogenicity in the flax rust fungus, *Melampsora lini*. On varieties of flax, *Linum usitatissimum* that have one gene for resistance to the avirulent parent race, F₂ cultures of the fungus segregate into monofactorial ratios. On varieties having 2, 3, or 4 genes for resistance to the avirulent parent race, the F₂ cultures segregate into bi-, tri-, or tetrafactorial ratios (20–22) respectively. This suggests that for each gene that conditions reaction in the host there is a corresponding gene in the parasite that conditions pathogenicity. Each gene in either member of a host-parasite system may be identified only by its counterpart in the other member of the system.
Because of the lack of uniformity in the criteria by which plant pathologists identify gene-for-gene relationships, Person, Samborski & Rohringer (66) discuss its numerous facets and present the following definition:

A gene-for-gene relationship exists when the presence of a gene in one population is contingent on the continued presence of a gene in another population, and where the interaction between the two genes leads to a single phenotypic expression by which the presence or absence of the relevant gene in either organism may be recognized.

In this review I shall attempt to show how studies of gene-for-gene relationships may be utilized to establish the means of variation in pathogenic fungi, to identify major genes conditioning vertical resistance, to develop resistant varieties, to elucidate the physiology of resistance and susceptibility, and to explain the co-evolution of host-parasite systems.

**Variation in the Pathogen**

*Diff erential varieties monogenic for rust reaction.*—Physiologic races of plant pathogens are identified by their interaction with a set of host varieties termed "differentials". Often the differentials have been selected by the trial and error method with no knowledge of the number or identity of the resistance genes in each. The original flax rust differentials were developed by this method (19). Information obtained from such a series of differentials is of limited value. For example, in 1940, the flax variety Koto was developed as a rust-resistant replacement for the variety Bison. While being increased, Koto was attacked by rust. Later it was discovered that North American races virulent on Koto had been collected prior to 1940. Although two of the differentials then in use possessed the Koto resistance gene, they also possessed additional resistance genes that obscured the virulence of the races on Koto.

A set of differentials in which each member possesses a single, unique resistance gene is most efficient and informative in studies on the classification and variation of plant pathogens. Numerous instances of variation in plant pathogens have been attributed to mutation, heterokaryosis, or parasexualism. Most lack a satisfactory genetic explanation. Knowledge of the pathogenicity genotype of the parental culture and of the variant, presumably derived from it, should give the investigator a more convincing basis for explaining how the variant developed. A prediction of the gene-for-gene hypothesis is that the pathogenicity genotype of a fungus culture can be established by a selfing study on differentials having single resistance genes.

A routine race identification test establishes the pathogenicity genotype of organisms having a haploid pathogenic phase. With organisms having a dikaryotic or diploid pathogenic phase, the routine race test identifies the recessive pathogenicity genes. The fungus must be selfed to determine the heterozygosity or homozygosity of the dominant genes.

By backcrossing to Bison, a variety that has been susceptible to all North American races of *M. lini*, and utilizing the selective pathogenicity of
various races, flax lines apparently monogenic for each gene conditioning rust reaction have been developed. Races are classified on 18 of these lines (24). Infection types 0, 1, and 2 are classified tolerant and 3 and 4 as susceptible. Additional monogenic lines may be used as supplemental differentials to identify sub-races.

Resistance genes occur as multiple alleles in five loci. The symbols L and M, used by Myers (60) to designate resistance genes in two loci, have been retained. Symbols K, N, and P designate genes lying in the other three loci. Of the 26 resistance genes that have been identified, 1 is in K, 12 in L, 6 in M, 3 in N, and 4 in the P locus.

by numerical superscripts (25). To show the specificity between host and parasite, the symbol for the resistance gene is used as a subscript to the symbols A and a, respectively, indicating avirulence and virulence in the parasite (Table 1).

**TABLE 1. PATHOGENICITY GENOTYPES OF RACES 22 AND 1 AND F1 CULTURE A OF RACE 22 × RACE 1 ON 16 FLAX RUST DIFFERENTIALS MONOGENIC FOR RUST RESISTANCE**

<table>
<thead>
<tr>
<th>Differential variety</th>
<th>Resistance genotype</th>
<th>Reaction* to F1 culture A</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Race 22</td>
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<tr>
<td></td>
<td></td>
<td>Race 22</td>
</tr>
<tr>
<td>Clay</td>
<td>KK</td>
<td>aKak</td>
</tr>
<tr>
<td>Ottawa 770B</td>
<td>LL</td>
<td>aLaL</td>
</tr>
<tr>
<td>Stewart</td>
<td>L²L²</td>
<td>A1A1L²</td>
</tr>
<tr>
<td>Kenya</td>
<td>L⁴L⁴</td>
<td>aLaLaL⁴</td>
</tr>
<tr>
<td>Wilden</td>
<td>L⁶L⁶</td>
<td>aLaLaL⁶</td>
</tr>
<tr>
<td>Birio</td>
<td>L⁶L⁶</td>
<td>aLaLaL⁶</td>
</tr>
<tr>
<td>Dakota</td>
<td>MM</td>
<td>aMAM</td>
</tr>
<tr>
<td>Williston Brown</td>
<td>M¹M¹</td>
<td>aMAM¹</td>
</tr>
<tr>
<td>Cass</td>
<td>M²M²</td>
<td>aMAM²</td>
</tr>
<tr>
<td>Victory A</td>
<td>M⁴M⁴</td>
<td>aMAM⁴</td>
</tr>
<tr>
<td>Bombay</td>
<td>NN</td>
<td>aNaN</td>
</tr>
<tr>
<td>Polk</td>
<td>N¹N¹</td>
<td>aNaN¹</td>
</tr>
<tr>
<td>Koto</td>
<td>PP</td>
<td>aPAp</td>
</tr>
<tr>
<td>Akmolinsk</td>
<td>PP</td>
<td>aPAp</td>
</tr>
<tr>
<td>Abyssinian</td>
<td>PP²</td>
<td>aPA²Ap</td>
</tr>
<tr>
<td>Leona</td>
<td>PP³</td>
<td>aPA³Ap</td>
</tr>
</tbody>
</table>

* R = resistant; S = susceptible.

Although Bison has been susceptible to all North American races of *M. lini* and has served as the universally susceptible differential in my studies, it

Kerr (45) found that the gene that conditions resistance in Bison
tralian race A lies in the L locus, and it has been designated L9. Because the monogenic differentials were derived from Bison backcrosses, those having resistance genes in the K, M, N, and P loci may possess gene L9. Therefore, these lines are not satisfactory for determining the pathogenicity genotype of the races nonpathogenic on Bison.

In the Linum-Melampsora system, resistance is invariably dominant and virulence is invariably recessive. A study on the inheritance of pathogenicity in the cross of race 22 × race 24 of M. lini was interpreted as indicating that virulence on the differential variety Williston Brown was dominant (21). A later study (30) indicated that this interpretation was erroneous.

Hybridization.—In the principal seed flax producing region of North America, flax rust overwinters only in the telial stage. Consequently, hybridization of the fungus is concomitant with the initiation of each year's infection. Controlled experiments have demonstrated the role of hybridization in pathogenic variability (20, 21, 25, 30). In a cross of race 6 × race 22 of M. lini (25), 54 pathogenically different races were identified in a population of 67 F2 cultures. The parent races differed in pathogenicity on 12 of the monogenic differentials. Had enough F2 cultures been studied, 212 or 4096 races could have been identified from this cross. Hybridization is an important means of pathogenic variation in the rust and other fungi having a sexual stage as part of their life cycle, e.g., smuts (36), powdery mildews (59), and apple scab (2, 5, 6). However, hybridization results only in a recombination of the genes already existing in the parental races.

Mutation.—New genes for virulence are the results of mutation. Numerous attempts to induce mutations to virulence in the rust fungi have been made, but because the results were negative few have been published. In most instances the investigator knew neither the number nor the identity of the resistance genes in the host varieties on which he attempted to screen his mutants, nor the pathogenicity genotypes of the urediospores that he sought to mutate. Since resistance and avirulence usually are dominant, the chance of detecting a mutation to virulence is slight when urediospores are screened on varieties having two or more resistance genes. In order to attack such a variety the urediospore would have to be virulent on all the respective resistance genes of the host. Furthermore, a mutation to virulence in a urediospore that is homozygous for the dominant avirulence genes can be detected only if the corresponding gene in each dikaryotic nucleus mutates.

Anderson & Hart (1) screened urediospores of race 48 of Puccinia graminis f. sp. tritici that had been subjected to several dosages of thermal neutron and X-radiation on four wheat stem rust differentials. No mutations in the rust were observed. Rowell, Loegering & Powers (71) irradiated urediospores of race 111, P. graminis tritici, and those of an F1 culture of race 111 × race 36. Although the cultures were phenotypically similar,
race 111 was of unknown pathogenic genotype, whereas the hybrid was heterozygous for pathogenicity on the variety Marquis. No mutants were recovered from screening the X-irradiated spores of race 111 on Marquis. Numerous mutants to virulence were obtained when the irradiated spores of the hybrid were screened on Marquis.

Varieties monogenic for resistance and a urediospore culture heterozygous for all genes for pathogenicity should be ideal for mutation studies. To obtain the closest approximation to this ideal, race 22 of *M. lini*, the race of widest virulence, was crossed with race 1, the race of narrowest virulence. Selfing studies showed that race 22 was homozygous for virulence on 14 and for avirulence on 2 differentials, while race 1 was homozygous for virulence on 1, homozygous for avirulence on 11 and heterozygous on 4 (Table 1). For example, since both parent races were avirulent on Bombay (*NN*), a urediospore of *F1* culture A of race 22 × race 1 would remain avirulent on Bombay even if an *A*M gene in one nucleus mutated to the recessive *a*N. The *A*N gene in the other nucleus would condition avirulence of that spore on Bombay. But the mutation of the dominant *A*M gene in the race 1 nucleus would make the spore homozygous for the recessive genes *a*M*a*M and should enable it to attack Dakota (*MM*).

To test this hypothesis, *F1* urediospores of race 22 × race 1 culture A of *M. lini* (Table 1) were subjected to X-irradiation at LD<sub>50</sub> and LD<sub>90</sub> and screened for mutations on the differentials monogenic for resistance (27). No uredia developed on Stewart or Bombay, the differentials to which the urediospores were homozygous for avirulence. Of the 154 uredia that developed on differentials to which the *F1* culture was heterozygous for pathogenicity, 94 produced sufficient inoculum for pathogenicity tests. Of these, 92 differed from the *F1* culture by virulence to the differential on which they were screened. This would be expected of one "hit" on the gene string. The other two cultures were virulent on an additional differential as would be expected of two "hits." Mutations to virulence on Birio (*L6*) and Cass (*M8*) were about 20 times as frequent as those on Koto (*P*) and Leona (*P3*). Spontaneous mutations were obtained only on Birio and Cass. This suggests a parallelism between rates of X-ray-induced and spontaneous mutations. In regions where they are effective, varieties having resistance genes to which the parasite shows a low rate of mutation to virulence may maintain their resistance for a longer period of time.

Schwinghamer (75) concluded that in race 1 of *M. lini*, induced mutations to virulence on the flax variety Dakota were due to a loss (deletion) of a chromosomal segment bearing the *A*M gene. I (28) selfed two of Schwinghamer's (74) race 1 X-ray-induced mutations to virulence on Koto. Each of the 198 selfed cultures was virulent on Koto and 16 were virulent on Abyssinian (*P2*) and Leona (*P3*), varieties to which race 1 was homozygous for avirulence (Table 1). Therefore, new genomes for virulence were induced in a rust culture by X-irradiation. The mutations were attributed to the deletion of that portion of the chromosome carrying the closely linked
genes for avirulence to Koto, Abyssinian, and Leona. The fact that the deletion of a dominant gene for avirulence changed the pathogenicity of a spore from avirulent to virulent is an important consideration in studies on the physiology of host-pathogen interaction.

**Heterokaryosis.**—Parmeter, Snyder, & Reichle (63) have reviewed the role of heterokaryosis in the variability of plant pathogenic fungi. They conclude that, except in the rust and smut fungi where heterokaryosis takes a special form of the dikaryon, the evidence is inadequate to support the hypothesis that heterokaryosis affects pathogenicity or virulence.

Fusions between germ tubes and hyphae in various rust fungi have been observed frequently. Pathogenic and color variants obtained by screening urediospore mixtures of two races of *P. graminis tritici* have been attributed to nuclear exchange through hyphal fusions or, if more than two new variants were isolated, to somatic hybridization or parasexualism (7, 16, 82-84). The pathogenicity genotypes of the parental cultures and of the variants derived from them were not established.

I screened four *F₁* urediospore cultures of race 22 × race 1 of *M. lini*, designated A, B, C, and D, singly and variously paired on three differentials that were highly resistant to all four cultures (29). Race 22 was homozygous for pathogenicity. Therefore, one nucleus in each *F₁* culture had the pathogenicity genotype of race 22 (Table 1). Since race 22 was virulent on the four differentials to which race 1 segregated for pathogenicity, a routine race test established the pathogenicity genotype of the race 1 nucleus in each *F₁* culture. Race 22 was recovered only when urediospores of *F₁* culture B were mixed with those of A, C, or D. This would be expected if the race 22 nucleus of culture B was of one mating type (+) and those of cultures A, C, and D of the other (−) and that the (+) and (−) race 22 nuclei became associated in one cell by nuclear migration through hyphal fusion. Some cultures were recovered that differed from one or another of the *F₁* cultures by increased virulence on the differential on which they were screened. This would be expected of a spontaneous mutation at a single locus for which the culture was heterozygous.

**Parasexualism or somatic hybridization.**—The experiments in which the paired *F₁* cultures of race 22 × race 1 were screened for pathogenic variants (29) served as a test for somatic hybridization as well as for heterokaryosis. Because of the numerous loci at which the *F₁* cultures were heterozygous for pathogenicity, variants virulent at several loci would have been expected if a parasexual process or somatic hybridization had occurred.

Ellingboe (16) has noted that some rust races are known to be heterozygous for several virulence genes. Since each race possesses a (+) and a (−) haploid nucleus it should be as capable of giving rise to variants through the parasexual process as a mixture of urediospores of two or more

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races. Yet variants ascribed to parasexualism have been derived only from race mixtures (7, 9, 16, 82–84).

Gene-For-Gene Systems

The gene-for-gene hypothesis was based on correlated genetic studies of both host and parasite (20, 25). For each gene that conditions resistance in the host there is a corresponding gene that conditions pathogenicity in the parasite. Acceptance of the hypothesis enables one to construct hypothetical genotypes of host and pathogen in the absence of direct genetic studies by determining the reaction of a range of host varieties to a range of pathogen races (64). The following examples illustrate some of the data upon which the gene-for-gene relationships in the host-parasite systems listed in Table 2 are based.

Triticum-Puccinia graminis.—Like the Linum-M. lini system, the Triticum-P. graminis gene-for-gene relationship is based on genetic studies of

<table>
<thead>
<tr>
<th>System and Reference(s)</th>
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<tbody>
<tr>
<td>Linum—Melampsora lini (20, 25)</td>
</tr>
<tr>
<td>Triticum—Puccinia graminis tritici (34, 43, 53, 86)</td>
</tr>
<tr>
<td>Triticum—Puccinia striiformis (87)</td>
</tr>
<tr>
<td>Triticum—Puccinia recondita (32, 73)</td>
</tr>
<tr>
<td>Avenae—Puccinia graminis avenae (54)</td>
</tr>
<tr>
<td>Coffea—Hemileia vastatrix (61)</td>
</tr>
<tr>
<td>Helianthus—Puccinia helianthi (72)</td>
</tr>
<tr>
<td>Avenae—Ustilago avenae (38)</td>
</tr>
<tr>
<td>Triticum—Ustilago tritici (62)</td>
</tr>
<tr>
<td>Triticum—Tilletia caries (56)</td>
</tr>
<tr>
<td>Triticum—Tilletia controversa (39)</td>
</tr>
<tr>
<td>Hordeum—Erysiphe graminis hordei (58)</td>
</tr>
<tr>
<td>Triticum—Erysiphe graminis tritici (68)</td>
</tr>
<tr>
<td>Malus—Venturia inaequalis (2, 6)</td>
</tr>
<tr>
<td>Avenae—Helminthosporium victoriae (85)</td>
</tr>
<tr>
<td>Solanum—Phytophthora infestans (77)</td>
</tr>
<tr>
<td>Lycopersicum—Cladosporium fulvum (11)</td>
</tr>
<tr>
<td>Solanum—Synchytrium endobioticum (41)</td>
</tr>
</tbody>
</table>

both the host and the dikaryotic parasite. Loegering & Powers (53) determined the inheritance of pathogenicity of 108 F$_2$ cultures of race 111 X race 36 on 20 wheat varieties. Their results indicated eight independently inherited genes for pathogenicity. On the variety Marquis, to which race 111 was avirulent and race 36 virulent, the F$_2$ cultures segregated into a ratio approximating 12 avirulent : 3 intermediate : 1 virulent. This indicated that
Marquis possesses two genes for resistance to the parent culture of race 111. Williams, Gough & Rondon (86) determined the pathogenicity of the parental, F₁ and F₂ cultures of Loegering & Powers on Little Club, Marquis, and on lines homozygous for single genes for resistance derived from Little Club × Marquis. Little Club was susceptible to all cultures. The tests confirmed those previously published (53). Both genes for avirulence are dominant and moderate avirulence is masked by high avirulence.

Green (34) found that virulence on Marquis lines carrying genes Sr₈, Sr₉a, Sr₉b, or Sr₁₁ is due to single recessive genes in each case and virulence on lines Sr₇ or Sr₁₀ is probably so controlled.

Kao & Knott (43) studied the inheritance of pathogenicity in the cross race 29 X race 111 on Marquis and Prelude lines carrying single genes for resistance to stem rust. Virulence on Sr₅, Sr₆, Sr₈, Sr₉a, Sr₁₄ and a gene in Marquis is recessive in a gene-for-gene relationship. However, virulence on Sr₁ is possibly controlled by two complementary dominant genes.

*Coffea-Hemileia vastatrix.*—Since the perfect stage of the coffee rust fungus is not known, studies on the genetics of its pathogenicity are not possible. By determining the pathogenicity of 12 races of the parasite to clonal lines and hybrids between clonal lines, Noronha-Wagner & Betten-court (61) were able to postulate the resistance gene or genes in the clonal lines and hybrids. They determined that resistance to *H. vastatrix* is conditioned by four dominant genes. Following Person's (64) method of analysis, they inferred the pathogenicity genotypes of the 12 races and predicted the likely occurrence of the four races not yet known.

*Triticum-Ustilago tritici.*—Oort (62) determined the reaction of eight variety groups of wheat to six physiologic races of *U. tritici*. He explained this study by assuming that two sets of resistance genes and two sets of incompatibility genes (dwarfing of susceptible plants but no smutted heads) in the host interacted with four sets of complementary genes for virulence in the parasite. Thus, he demonstrated a gene-for-gene relationship in this host-parasite system without studying the genetics either of resistance in the host or pathogenicity in the parasite.

Halisky (36) has reviewed the occurrence and significance of other gene-for-gene relationships in the smut fungi.

*Hordeum-Erysiphe graminis* and *Triticum-Erysiphe graminis.*—The genetics of host-pathogen interaction in the powdery mildews has been reviewed by Moseman (59). He (58) and Powers & Sando (68) extended the gene-for-gene hypothesis to the powdery mildews. Since the pathogenic phase is haploid, all cultures are either A (avirulent) or V (virulent). Moseman (58) crossed a culture of *E. graminis* f. sp. *hordei*, virulent on the barley varieties Goldfoil and Kwan, with one avirulent on each variety. Resistance in each variety was conditioned by a single gene. The F₂ cultures
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segregated for pathogenicity into the 1:1:1:1 ratio predicted by the gene-for-gene hypothesis. Powers & Sando (68) in a somewhat similar study found that for each of the two genes conditioning resistance in the wheat variety Normandie there were corresponding genes for virulence in *E. graminis* f. sp. *tritici*.

*Malus-Venturia inaequalis.*—Boone & Keitt (6) studied the inheritance of pathogenicity of 10 parent lines of *V. inaequalis* on 15 apple varieties. Their results indicate that 7 different gene pairs condition lesion (susceptible) and fleck (resistant) reactions. From the reactions of the avirulent alleles they postulated the number and identity of resistance genes carried by seven differential apple varieties. In subsequent studies (2, 5), 19 independently inherited pathogenicity genes have been identified. Boone (5) presents a comprehensive discussion of the genetics of *V. inaequalis* in this volume.

Flangas & Dickson (18) and Berry (3) studied the *Zea-Puccinia sorghi* system. They reported that pathogenicity of *P. sorghi* was not inherited in a Mendelian manner and postulated "gene pools" or "indeterminate inheritance" to explain their results. These are the only reports of nonMendelian inheritance of pathogenicity to specific or major genes for resistance of which I am aware. Berry suggested that a larger number of inbred clones of one line be studied and that failure to obtain consistent infection on *Oxalis* spp. with teliospores is a major difficulty. This suggests that lethal genes may be associated with repeated selfing of *P. sorghi*, and that the populations studied were not random samples.

The rust differentials were lines of corn monogenic for resistance (18). However, Hooker (40) observed that nearly all corn grown in the United States possesses generalized or polygenic resistance. Perhaps more consistent results could be obtained by the use of differentials in which monogenic resistance had been added to a variety lacking both specific and generalized resistance. Such differentials would also possess the same cytoplasmic background.

**Development of Resistant Varieties**

The control of plant diseases by breeding for resistance has been the subject of several recent reviews (8, 12, 13, 40). In these, the advantages and limitations of the use of major gene resistance, polygenic resistance, and multiline varieties have been adequately discussed.

**Identification of new major resistance genes.**—In the North Central States flax rust has been satisfactorily controlled by major resistance genes. In fact, polygenic resistance has not been demonstrated. This may be because it has not been actively sought. Since 1940, six genes, then considered to condition resistance to all North American races of *M. lini*, have become ineffective. Varieties in which these genes condition the resistance have suc-
cumbed to new races or to races that had remained undetected until a variety dependent on a particular gene for its resistance became widely grown. Although there are seven genes that condition resistance to all known North American races, additional sources of rust resistance are sought.

New material for testing is provided by the Plant Introduction Service, USDA. Genes for rust resistance can be distinguished by tests for allelism, differences in their resistance phenotype, and the selective pathogenicity of physiologic races of the parasite. Six of the seven genes that condition resistance to _M. lini_ in North America are ineffective against the widely virulent South American race 22. _F_2 cultures of race 22 crossed with North American races have been effective in isolating and identifying unknown resistance genes (22, 26).

_Development of varieties multigenic for resistance._—In the flax-flax rust system, virulence has been recessive and resistance dominant. A new race can attack a heretofore resistant variety only if it is virulent on all of that variety's resistance genes. The probability that a race will become homozygous for two or more new virulence genes is much less than that it will do so for one pair. Therefore, varieties with two or more genes for rust resistance should be less apt to succumb to new races than varieties possessing a single resistance gene.

Flax varieties having almost any combination of resistance genes, within the limits of allelism, may be developed by utilizing the selective pathogenicity of races of _M. lini_. Since the flax plant grows by the unfolding of a terminal bud, the resistant genes in each plant of a hybrid progeny may be ascertained by successive inoculation at approximately weekly intervals with races that identify the respective genes. For example, all plants in the progeny of a cross of _L_6 × _M_3 that are resistant to race 218, (virulent on _L_6 and avirulent on _M_3) possess the gene _M_3. Likewise, all plants resistant to race 106 (virulent on _M_3 and avirulent on _L_6) possess gene _L_6. Plants resistant to both races possess both genes. Lines carrying three genes for resistance to all North American races of _M. lini_ were developed by applying the principle that each resistance gene in a hybrid progeny is identified by inoculation with a race avirulent to that gene but virulent on all other resistance genes involved in the cross (25, 31).

Studies of _F_2 populations indicate that the rust-resistance genes in flax occur as multiple alleles in five loci (25). A more efficient test for allelism is a study of testcross populations (55). I (30) studied testcross progenies involving resistance alleles in the _L_, over was obtained in tests of more than 30,000 plants of the _L_ heterozygotes. Likewise, no crossovers were obtained in tests of 7354 _PP_1 × _pp_ and 2306 _PP_3 × _pp_ plants. Resistance genes lying in the _L_ and _P_ loci are either alleles or very closely linked. Crossing over in progenies of _MM_1 × _mm_, _MM_3 × _mm_, and _MM_4 × _mm_ ranged from 0.17 to 0.39%. In a test of 9115 _NN_1 × _nn_ plants, 0.11% crossing
MM4, and NN1 were derived from the dominant gene crossovers.

Genes for pathogenicity on lines of flax possessing genes M, M3, M4, N, and N1 are independently inherited. The MM3, MM4, and NN1 resistance genes are so closely linked that each pair would have been regarded as a single gene in screening tests of varieties to serve as flax rust differentials. Had differentials possessing genes MM3, MM4, or NN1 been used in pathogenicity tests of F2 cultures (21, 25), ratios approximating 15 avirulent:1 virulent would have been obtained. This would have been interpreted as an instance in which two complementary genes in the parasite conditioned pathogenicity on a differential possessing a single gene for resistance—an exception to the gene-for-gene hypothesis.

Induction of rust-resistant mutants by irradiation.—Reports of the successful induction of disease-resistant mutants was reviewed by Konzak (48). Later studies (10, 46) suggest that the earlier reports be reassessed and that tests be conducted under more rigid standards of isolation.

The variety Bison, which has no genes for resistance to North American races of M. lini, and Bison backcrosses monogenic for resistance were used in a study on induced mutations (Flor, unpublished). Seed was produced in the greenhouse at Fargo, North Dakota. The parental plants were tested for purity with appropriate races. Outcrossing has never been observed in plants grown in the greenhouse. These seeds were irrigated by Drs. Calvin Konzak and Seymour Shapiro at the Brookhaven National Laboratory.

In preliminary field tests of several lines monogenic for rust resistance, up to 10% of the plants in some irradiated progenies were resistant to races to which the parent was susceptible. Many of the plants from irradiated seed were obviously damaged. Frequently the anthers did not dehisce nor the filaments elongate. When this occurred the petals, which are usually shed within two to three hours of opening, adhered most of the day and attracted flying insects. All the “mutants” tested proved to be resistance genes from adjacent plantings.

In another trial, seed of the monogenic differential Cass (M3), that had been subjected to dosages of 35,000 and 40,000 r was sown in a wheat nursery. All except two plants in the 734 progenies had the reaction of the parent. These two plants were resistant to race 107, virulent on Cass. Genetic studies showed them to be heterozygous for resistance gene N1. Gene N1 conditioned a resistance in a line of flax that was increased in a plot more than 200 m from the wheat nursery. Obviously, excessive care to avoid natural crossing is warranted in attempts to induce mutations for resistance in plants.

Seed of a Bison plant was increased in the greenhouse during the winter of 1956–1957. This seed, subjected to X-ray dosages of 60,000, 80,000 and 100,000 r, was sown in field plots at Brookhaven National Laboratory, Long Island, N.Y. These plots were remote from any known commercial or ex-
experimental flax. Dr. Konzak harvested these plots and sent the seed to me for testing. I determined the reaction to race 1 of *M. lini* of more than 375,000 X$_2$ plants in the greenhouses at Fargo from 1958 to 1969. Race 1, virulent on Bison, is the race of narrowest virulence and consequently the best race available to detect a mutation to resistance in Bison. Mutations for color of the petals, chlorotic sectors and loss of vigor were observed but none for rust reaction.

Dominant and beneficial mutations in flax induced by X-irradiation are rare. However, nature operates on an almost infinitely greater scale than man, and mutation offers the most plausible explanation for the diversity of rust-resistant germ plasm in flax.

**Epidemiology**

Browning & Frey (8) and Watson (82) reviewed numerous reports on the relation of virulence to survival of plant pathogenic fungi. Virulence usually is recessive and most reports agree with the hypothesis that physiologic races having wide host ranges compete poorly with races having a narrower host range on nonresistant varieties (79). This may be an oversimplification as undoubtedly there are numerous other factors involved in aggressiveness or fitness of pathogenic strains to survive.

The flax-flax rust system is well suited for a study of the survival of simple (few genes for virulence) and complex (many genes for virulence) races under field conditions. The pathogen is autoecious and, in the North Central States, each year's infection is initiated through the sexual phase. Browning & Frey (8) have outlined such an experiment.

I (23) identified the virulence (homozygous recessive) genes in each race of *M. lini* isolated from field collections during 1931-1951. The predominant races carried the least number of virulence genes that permitted survival of an obligate parasite. The percent of races with unnecessary virulence genes declined during the period of the study. A comparison of the 1931-1951 surveys with those of 1964-1968 (Flor, unpublished) supports this conclusion. However, it shows the influence of the resistance genes in varieties that were grown during each period.

When a wheat variety is attacked by new races of stem rust the breeder often adds a new resistance gene to its resistance genotype (82). In order to attack the new variety, a rust strain must retain its virulence to the old variety with added virulence to the new gene. With flax, the new resistance gene has replaced rather than been added to the rust-resistance genes in the old variety. Rust resistance has been conditioned by a single gene in each of the widely grown commercial varieties that have succumbed during the past 30 years. To attack a new flax variety, only the virulence gene that will overcome the new resistance gene is needed.

An unnecessary resistance gene is one of which there is no record that it has conditioned rust resistance in a commercially grown variety in the
North Central States. Bison, susceptible to all North American races of *M. lini*, was the predominant variety from 1931 to the early 1940s. Rust collections made during this period may be regarded as random samples. In the 1940s Bison was replaced by Koto (*P*), Dakota (*M*), and Marine (*L*). Thereafter, races collected in the field necessarily were virulent on one of these varieties. Races attacking Koto, Dakota, and Marine, respectively, were first found in 1940, 1948, and 1962. In some years, no rust was observed in commercial fields following the introduction of resistant varieties, and a sizeable proportion of the cultures studied were from experimental plots.

The immediate and residual effect of a resistance gene on virulence of collections is related to the popularity of the variety. Koto was not as widely grown as Dakota. Koto was susceptible to 24% of the rust collections made during 1942–1947 when the Bison acreage was declining. During 1948–1951, when Dakota was the most widely grown variety, Koto was susceptible to 51% and Dakota to 79% of the collections. By 1954 both Koto and Dakota had been largely replaced by other resistant varieties. Koto was susceptible to 34% and Dakota to 60% of the collections made during the 1964–1968 period. Thus, if a virulence gene becomes established in a rust population, it apparently persists for many years, although it is no longer essential to the survival of the parasite.

Cultures identified as having unnecessary genes for virulence declined from 65% of the 1931–1947 collections to 17% of those made during 1964–1968. By way of contrast, 90% of the 1931–1947 cultures possessed none or one pair of recessive genes whereas 94% of the cultures studied from 1964 to 1968 had two or more such pairs. This agrees with Watson's (82) observations that genes for virulence continually increase as they overcome the resistance genes in popular varieties.

None of the cultures studied during 1964–1968 was virulent on the monogenic differentials possessing genes *K*, *L*₂, or *N*. These differentials were susceptible to some of the races identified during 1931–1951 (23). It is not known if genes for virulence on these differentials have disappeared from the flax rust population. They may remain as undetected heterozygotes.

Although they are not conclusive, the studies with flax rust tend to support the thesis that aggressiveness is associated with dominant avirulence genes. Flax rust is a destructive disease in Argentina (78) and Egypt (communication from O. I. Selim, Sakha Research Station, Kafr-El-Sheikh, U.A.R.). In both areas most races are virulent on more than 20 differentials. If mutations to virulence are the result of chromosomal deletions (28, 74) is it likely that 20 deletions short enough to exclude vital functions should occur? More than one-third of the X-ray-induced mutations to virulence failed to produce sufficient spores for a pathogenicity test (27). Further studies of the correlation between a narrow pathogenicity spectrum and aggressiveness or vigor should be made.
Nature of Resistance

The nature of specific or major gene resistance in the rusts and powdery mildews is one of the most challenging yet elusive problems in plant pathology. What are the mechanisms whereby the genes in the host and the parasite interact to control the development of the disease? Chemical, morphological, or physiological variations observed between phenotypes that differ only in one gene for resistance are more apt to be related to resistance than variations observed between phenotypes that, in addition to the gene for reaction, differ in many other genes. The flax rust differentials, essentially monogenic for resistance, have been backcrossed to Bison as many as 15 times. Races of the parasite that differ by a single gene for virulence may be identified by a routine test on the differential lines monogenic for resistance (24). Also, mutant lines of the pathogen that differ from the parental culture by a single virulence gene were developed by irradiation (27, 74). The Bison backcrossed lines and cultures of M. lini that differ by single genes for virulence have been used in studies on the nature of resistance and susceptibility.

Doubly et al (15) compared the globulin antigens of four races of M. lini with those of the rust-susceptible variety Bison and selections of the seventh backcross with Bison of the monogenic differentials Cass, Koto, and Ottawa 770B. Their results indicated that avirulence and virulence were related to resistance and susceptibility through the specific rust antigens. A host variety was susceptible to a race of the pathogen when it contained, as a minor antigenic component, a protein serologically related to one of the proteins characterizing that particular race. Doubly and I have confirmed these results in tests (unpublished) in which the urediospores of the four races were produced on Bison. Thus, it is unlikely that rust spores carried over host antigens.

Studies with nonobligate parasites give some support to the common antigen hypothesis (14). Races of Xanthomonas malvacearum, the cause of angular leaf spot of cotton, to which the host was susceptible, had more antigens in common with cotton leaves than did nonpathogenic races.

Knott (47) used the agar-gel diffusion plate method to study the proteins in stem rust spores and in lines of Marquis wheat carrying single genes for resistance. In contrast to the cases mentioned above, he found no association of an antigen with a particular gene for resistance and could detect no antigens common to both host and parasite. The serology approach needs further study before any definite statement can be made concerning its validity.

Hadwiger & Schwochau (35) propose an induction hypothesis to explain the gene-for-gene mechanism in flax and flax rust. The dominant genes in the pathogen direct the synthesis of compounds that activate the corresponding dominant genes in the host. The activated host genes affect an alteration or disintegration of the cellular organization of the host that results in a hypersensitive type of response. Tests of the induction hypothe-
sis with the flax-flax rust system are being made by Hadwiger and associates.

Support of the induction hypothesis (35) was provided by Littlefield (51), who showed that flax rust infection is significantly reduced as a result of prior inoculation with an avirulent race of the pathogen. The induced resistance caused a reduction in the number, size, and rate of development of uredia by the normally pathogenic race. That study as well as subsequent investigations on the histology of flax rust resistance (52) suggest that diffusible substances from the pathogen may be responsible for triggering the resistance reactions.

**Co-evolution of Host-Parasite Systems**

Parasitism is an antagonistic rather than a mutualistic form of symbiosis. Unopposed selection for aggressiveness in the parasite would lead to elimination of the host. Unopposed selection for resistance in the host would lead to elimination of the parasite.

Mode (57) applied modern genetic concepts to the problem of microevolution in parasitic systems. He proposed a mathematical model that incorporates specific gene-for-gene relationships to explain the co-evolution of hosts and their parasites. He assumed that during their evolution, flax and the small grains were open pollinated. If host and parasite evolved together, the genic systems controlling their interaction have been established by the selective pressure exerted by one on the other. Mode's model, in addition to specific gene-for-gene interactions in host and parasite, assumes allelism of resistance genes, and independently inherited pathogenicity genes. He demonstrated that, under certain conditions, parasitic systems having these characteristics would be in equilibrium, thus assuring the survival of both host and parasite.

Resistance in the host usually is dominant, and the resistance genes often occur as multiple alleles. Virulence in the parasite is usually recessive, and the genes for pathogenicity are independently inherited. Therefore, most parasitic systems possess the essential features included in Mode's mathematical model of co-evolution.

Theoretical consideration of the origin of gene-for-gene relationships led Person (64, 65) to conclude that relationships such as that postulated for *Linum-Melampsora* should be the rule rather than an exception in host-parasite systems. This kind of relationship is an automatic result of mutation and natural selection for resistance in the host and for virulence in the parasite. Analysis of the data available for the *Solanum-Phytophthora* system showed it to be ideal to illustrate the properties inherent in gene-for-gene systems and to illustrate a new method of analysis for these properties.

Person (64) constructed a theoretical model of host-parasite interactions with gene-for-gene relationships, at five pairs of loci. With a dichotomous classification such as that used by Black et al (4), and with 5 genes for resistance this model differentiates $2^5$ or 32 races. However, if one of
the five differentials carries two resistance genes (e.g. $R_1$, $R_2$, $R_3$, $R_4$, and $R_5$, in the respective varieties) only 24 races can be identified. Another feature of Person's theoretical model, which contained host varieties with 5, 4, 3, 2, 1, and 0 resistance genes, is that the number of races virulent on these varieties increase geometrically, 1, 2, 4, 8, 16, 32. Only one race attacks the variety with five resistance genes, etc. The variety lacking a gene for resistance is susceptible to all 32 races.

Person (64) analyzed my data on races of $M. lini$ (24) in accordance with his theoretical model and concluded that many of the flax rust differentials, that I had presumed to be monogenic for resistance, possess two or more resistance genes. Johnson (42) has shown that evolution in the plant rusts is man-guided. In $M. lini$ this may be illustrated by the pathogenicity of races obtained from different flax growing regions on the flax rust differentials carrying the four alleles for resistance in the $P$ locus.

The differential varieties, Koto, Akmolinsk, Abyssinian, and Leona, that respectively, carry resistance genes $P$, $P^1$, $P^2$, and $P^3$ were susceptible to all Argentine races of $M. lini$ described by Vallega & Antonelli (78). Had Person's study been confined to Argentine races, no $P$ resistance genes would have been detected and the four differentials possessing genes in the $P$ locus could have served as universally susceptible varieties.

All four $P$ differentials are highly resistant to Australian race A (81). Tests with this race could be explained by assuming that the same gene conditions resistance in each differential carrying a gene in the $P$ locus.

Koto is highly resistant and Akmolinsk, Abyssinian, and Leona are susceptible to most Australian races other than race A (44). These races identify only the resistance gene in Koto. The three other differentials having a $P$ resistance gene would have been regarded as universally susceptible varieties.

Koto and Leona have been highly resistant and Akmolinsk and Abyssinian susceptible to all Oregon races. In tests with Oregon races, the same resistance gene would have been assigned to Koto and Leona. Akmolinsk and Abyssinian, being susceptible, would have no recognizable resistance gene.

The four varieties having resistance genes in $P$ locus have been differentiated by races collected in the North Central States. I have identified hundreds of collections of urediospores from this region that attack Koto and hundreds that attack Akmolinsk, but none that attack both differentials. This was interpreted as indicating that, in this region, virulence on Koto and Akmolinsk is conditioned by closely linked genes in the repulsion phase.

Genetic studies (28) have verified this interpretation. Races to which Akmolinsk is susceptible produce resistant infection type 1 (24) on Abyssinian in contrast to the near immune infection type 0 produced by races to which Akmolinsk is resistant. Leona has shown practical immunity to all urediospore collections from the North Central States.

These studies indicate that single genes in the $P$ locus condition resis-
CURRENT STATUS OF THE GENE-FOR-GENE CONCEPT

stance in Koto, Akmolinsk, and Leona. Abyssinian could, although not necessarily, possess two genes, the Akmolinsk gene $P^1$ plus an additional closely linked gene.

Person (64) recognized the possibility of man-directed evolution and excluded some races from his analysis. His sample of 179 races in a system of 16 resistance genes is inadequate. Furthermore, 131 of the 179 races that comprised his population were hybrids of the narrowly virulent North American races 6 or 24 with the widely virulent South American race 22. Many of the deviations from Person's model can be accounted for by simple Mendelian segregation in these hybrid populations.

The investigator's dependence on the avirulence gene complement of a pathogen to resolve and identify the resistance gene complement of a host may be further illustrated from studies of resistance to stem rust in the wheat variety Marquis. Puttick (70) reported that resistance in Marquis to race 19 is conditioned by a single gene. Williams et al (86) found that Marquis possesses two genes for resistance to one culture of race 111 and three genes for resistance to another. Sheen (76) identified at least four resistance genes in Marquis substitution lines of the wheat variety Chinese Spring.

Fincham & Day (17) point out that there can be no conclusive proof of the correctness of Person's hypothesis except through conventional genetic analysis of host and parasite. The primary centers of origin of many cultivated plants is well established (50). It was in these gene centers that both host and parasite evolved and developed a biological balance. The primary gene center has been and probably will continue to be the plant breeder's principal source of both vertical and horizontal or polygenic resistance. Resistance may be obtained from the cultivated host plants or their wild progenitors. Many primary gene centers have been extensively explored for resistant host germ plasm, but the pathogenic range of the accompanying parasites is unexplored (50). The Solanum-P. infestans system is an exception in that both host resistance and pathogenic diversity have been studied in their centers of primary origin (33). This system conforms ideally to Person's (64) analysis.

Experimental data to examine Mode's (57) or Person's (64) hypotheses on the co-evolution of host-parasite systems are difficult to obtain. Cultivated plants and their parasites evolved over a long period of time and left few records. Mode assumed that the hosts: wheat, oats, barley, flax, etc. were open pollinated during their evolution. Today, these crops are rather closely self-pollinated. Much evidence supports the assumption that aggressiveness and wide virulence are negatively correlated (23, 49, 79, 82) but some data contradict it (54, 82). Modern man, by his breeding program and transportation of plants and their pathogens throughout the world, has upset Nature's balance and has impeded the study of the co-evolution of host and parasite.

Horizontal resistance or multigenic resistance may have had a role in
maintaining the biological balance between host and parasite throughout their evolution. Most cultivated plants and their wild progenitors in primary centers of origin possess some degree of horizontal resistance to endemic pathogens (50). During their evolution, host plants that possessed a new gene for vertical resistance should have had a survival advantage. That this advantage was temporary and of limited value is shown by the diversity of disease-resistant germ plasm that persists in plants obtained from these areas of primary origin. Seedlings of plants possessing horizontal resistance often are relatively susceptible to parasites, especially the plant rusts. This permits the fungus to become established early in the growing season when the amount of inoculum is limited. The host plant becomes more resistant as it grows and as the inoculum increases. Mature plants possessing only horizontal resistance rarely have the immunity conferred by many genes conditioning vertical resistance. This permits the continued development of the parasite with minimum damage to the host. Thus, a state of equilibrium is established between host and parasite that assures the survival of both. It may explain the survival in the centers of primary origin of the many resistance genes that developed during the evolution of the host, as well as that of plants lacking genes for vertical resistance.

Disease epidemics that are familiar in today's agriculture rarely occur in nature (67). These epidemics develop as a result of man's interference. In his varietal breeding program he has either ignored horizontal resistance or subjected a host species, such as Pinus strobus, which evolved in North America, to a parasite, Cronartium ribicola, which evolved in Central Asia.

**Concluding Remarks**

The gene-for-gene hypothesis is applicable to most host-parasite systems in which resistance is conditioned by major (vertical resistance) genes, and virulence increases in a step-wise fashion. A recent interesting extension of the gene-for-gene hypothesis is the study of Hatchett & Gallun (37). They found that the ability of specific races of Hessian fly to survive on certain wheat varieties is controlled by genetic systems in the host and insect that are complementary. There is a gene-for-gene relationship between each gene for resistance in a wheat variety and a gene for survival in a race of the insect. This is the first report of gene-for-gene relationships between plants and insects. Similar relationships may exist between other insects, nematodes, bacteria, and viruses and their plant hosts.

The gene-for-gene concept has been useful as a tool to identify the roles of hybridization, mutation, heterokaryosis, and somatic hybridization in pathogenic variation of parasitic fungi. Also, it has served to survey and identify the resistance germ plasm in the host, to study induced mutations to resistance, and to developmultiline and multigenic varieties. Most data indicate that races of wide virulence compete poorly with races of narrow virulence on varieties susceptible to both. However, races having a wide viru-
Aggressiveness may not invariably be associated with restricted virulence, and the possibility that a super-race may develop on multiline and multigenic varieties warrants further study.

Hypotheses based on the gene-for-gene concept have been proposed (57, 64) to explain the co-evolution of host plants and their parasites. In these hypotheses no consideration is given to the possible role of horizontal resistance in co-evolution. Actually, there have been few recent studies in which resistance has been attributed to minor or polygenes that condition horizontal resistance (67). Some instances of resistance formerly attributed to polygenes have subsequently been found to be conditioned by major genes. Also, the incorporation of several genes for vertical resistance into a plant may confer to it a degree of horizontal resistance. While there are major genes that condition only vertical resistance and polygenes that condition only horizontal resistance, there is an overlapping area that needs resolving.

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