# *Phytophthora infestans*: New Tools (and Old Ones) Lead to New Understanding and Precision Management

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Annu. Rev. Phytopathol. 2016. 54:529–47

First published online as a Review in Advance on June 17, 2016

The *Annual Review of Phytopathology* is online at phyto.annualreviews.org

This article's doi: 10.1146/annurev-phyto-080615-095951



## Keywords

late blight, population, migration, phenotype, genotype, field, gene expression

## Abstract

New tools have revealed that migrations of *Phytophthora infestans* have been a dominant feature of the population biology of this pathogen for the past 50 years, and maybe for the past 170 years. We now have accurate information on the composition of many *P. infestans* populations. However, migration followed by selection can lead and has led to dramatically rapid changes in populations over large regions. Except for the highlands of central Mexico, many populations of *P. infestans* have probably been in flux over the past several decades. There is some evidence that this pathogen has different characteristics in the field than it does in the lab, and early field phenotypic analyses of hypotheses concerning fitness and pathogenicity would be beneficial. The newly available capacity to acquire and process vast amounts of weather and weather forecast data in combination with advancements in molecular diagnostics enables much greater precision in late blight management to produce recommendations that are site, host, and pathogen specific.

## INTRODUCTION

*Phytophthora infestans*, the causal agent of potato and tomato late blight, has been a major concern in agroecosystems since the mid-1840s. At times, the impact of this plant disease on humans has been devastating, with the most horrific example being the Irish potato famine that began in the mid-1840s (5, 57, 87). The enormity of the damage caused by this pathogen has compelled many scientists over the centuries to investigate its biology and to search for technologies to mitigate the effects of the disease. Initially, mainly plant breeders and epidemiologists were particularly interested, but as modern tools have been developed, molecular biologists have made great progress in deciphering how *P. infestans* interacts with host plants (53). Despite historical frustration (26, 63), optimism runs high that eventually we will use durably resistant plants (85) as the major component in late blight management.

*P. infestans* and late blight have been the subjects of intense scrutiny since the mid-1840s, with much learned about both. Annually, there are now more than 3,000 articles devoted to this organism and the disease it causes (28). During the past century, we have learned a tremendous amount about the epidemiology of the pathogen (15, 47, 48, 67); thus, we can often accurately predict when late blight is likely to be severe. As a result, late blight is managed much more effectively now than it was 100 years ago. However, despite our understanding of the environmental effects on the pathogen, there continue to be outbreaks of the disease that are more severe than expected. Some of these disease control failures have occurred recently (12, 32, 35). Obviously, we have much yet to learn.

It is the purpose of this review to illustrate how new tools have contributed to our improved understanding of populations of *P. infestans*, to suggest that combinations of new and old tools can lead to a more comprehensive and accurate understanding of the biology of *P. infestans* in the field, and to illustrate how these tools can lead to precision management.

## NEW TOOLS AND POPULATIONS OF *PHYTOPHTHORA INFESTANS*

Early on, very little was known about populations of *P. infestans*, largely because of a dearth of stable genetic markers. Before the 1980s, only specific virulence and mating type were available as markers. We now know that specific virulence is a remarkably variable trait, with some individuals of common pathotype being dissimilar genetically and some individuals within the same clonal lineage having diverse pathotypes (38, 81). Thus, it can be risky to infer genetic relationships among individuals using specific virulence as the only marker.

### New Tools: Biochemical and Molecular Genetic Markers

The development of biochemical and molecular markers has enabled investigators to distinguish genotypes with some clarity, and this has led to a much clearer view of populations of pathogens. These markers include allozymes (82), RFLPs (restriction fragment length polymorphisms) (39), mitochondrial haplotypes (8, 16), and microsatellites or simple sequence repeats (SSRs) (59, 60). For more detailed investigations, techniques such as genotyping by sequencing (GBS) (21) or gene sequencing (19, 43) have been used. The general assumption is that these markers are neutral and therefore not under selection. When a group of markers is available, multilocus genotypes (MLGs) can be constructed. Clearly, individuals with different MLGs are different from each other. In strongly clonal asexual populations, individuals of the same MLG can often be regarded as derived from the same progenitor and therefore in the same clonal lineage. Individuals in a clonal lineage differ from each other by mutation only and not by recombination (1). Interestingly, we

now know that some clonal lineages can differ from each other in pathogenicity traits. For example, some clonal lineages are equally pathogenic to potato and tomato, whereas others are primarily pathogenic on one or the other (17, 40). We have also just learned that some genotypes/lineages may have diverse reactions to certain environmental variables (G. Danies & W. Fry, unpublished results). Some clonal lineages have become quite famous (e.g., US-1, US-8, 13_A2, as illustrated below). There are, however, at least two cautionary notes. (*a*) If MLGs are defined on the basis of too few markers, individuals with the same MLG may actually be different. (*b*) In a very diverse (sexual) population, diverse individuals could share the same MLG by chance.

Using biochemical and molecular markers, it has become possible to identify migrations of *P. infestans* and to distinguish asexual from sexual populations.

## New Understanding: Migrations

Using molecular and biochemical markers, we have learned that migrations have played a huge role in the global population biology of *P. infestans.* Certainly, the first appearance of late blight in the United States (circa 1843) (79) was due to migration. We do not know how *P. infestans* first arrived in the United States during (or before) 1843 or how *P. infestans* arrived in Europe during (or before) 1845. In contrast, we do have reasonable scenarios to explain the migration that led to the displacement of the US-1 clonal lineage from most locations worldwide. By the mid-twentieth century, population analyses indicated that most populations worldwide were dominated by US-1 (38). In the latter part of the twentieth century, US-1 was displaced in many locations globally because of a migration initiated in the late 1970s. In retrospect, the first hint of this migration was the discovery of A2 mating type individuals in Switzerland in 1982 (50). Further analysis revealed that not only were there A2 mating types, but the entire population in northwest Europe changed in the 1980s and 1990s (33). A new population from Mexico displaced the US-1 clonal lineage in northwest Europe during the 1980s and into the 1990s (30, 33, 69). From Europe, individuals in this new population were moved to Asia, Southeast Asia, the Middle East, and North Africa (34). As of the early twenty-first century, US-1 remains dominant in southern Africa (71). US-1 was also displaced in the United States during the 1980s and 1990s, but the migration event that led to this displacement was distinct from the migration that introduced a complex population of *P. infestans* into northwest Europe in the late 1970s (37). As result of migration into Europe from Mexico, and into the United States from Mexico, late blight became dramatically more serious to the extent that there were reports in the American and international presses (18, 58).

Often the introduction of a new population (or clonal lineage) of *P. infestans* into a location is accompanied by more serious disease and sometimes with very negative economic and social impacts. Unfortunately, there are too many such examples, illustrated most recently by unexpectedly severe late blight in West Bengal, India (S. Guha Roy, personal communication). West Bengal State is the second largest producer of potatoes in India and supplies potatoes to neighboring states in eastern and northern India. A severe late blight epidemic in 2014 followed a year of very low prices (due to oversupply caused by a huge crop). The oversupply and low prices put financial pressure on potato farmers in the region, forcing many to borrow to stay in production. The severe late blight in 2014 was caused by an immigrant strain, 13_A2 (S. Guha Roy, personal communication). The very severe epidemic in 2014 increased the stress on farmers and unfortunately led to many farmer suicides (S. Guha Roy, personal communication) (**Figure 1**).

The most important mechanism of migration is via potato seed tubers infected by *P. infestans*, which are shipped long distances under conditions that assure the safe arrival of the tubers (and *P. infestans*). Trade in seed tubers is global, and strains of *P. infestans* detected in a potato seed tuber production area often can be subsequently detected in the location to which the tubers


**Figure 1**

Headlines from newspapers in West Bengal State, India, reporting the effects of severe late blight in 2014. As result of a potato shortage, exports from West Bengal to a neighboring state (Orissa) were reduced by West Bengal government regulation; the reaction in Orissa was that potato production was increased. The headline in Bengali states: "Increase in Potato Production by Orissa, Apprehension of Loss for this State" (personal communication from S. Guha Roy, West Bengal State University). Used with permission from S. Guha Roy.

were shipped. This mechanism is the logical explanation for the movement of US-8 (detected throughout the eastern United States in 1994) to the western part of the United States in 1995 (31, 52), and for the recent appearance of 13_A2 in India (11, 12) and China (61).

Although the transport of infected potato tubers has long been the dominant mechanism by which *P. infestans* is transported long distances, there are now examples of infected tomato transplants being shipped long distances, with the consequence of shipping *P. infestans* long distances. A very visible example occurred in the northeastern United States in 2009. In that case, transplants infected with the US-22 clonal lineage of *P. infestans* were sold in many large retail stores in several states in late June and early July 2009 (35). At the start of the epidemic, only transplants from a single supplier in large retail stores were infected. Thus, in late June, transplants infected with the US-22 clonal lineage were planted in home gardens throughout the northeastern United States, initiating a major tomato late blight pandemic (35). Interestingly, US-22, the clonal lineage responsible, is not noticeably more aggressive than many other clonal lineages and has subsequently nearly disappeared from the *P. infestans* population in the United States (28). The severity of the 2009 epidemic thus resulted from a massively extensive distribution of US-22 at the beginning of the season rather than the introduction of a particularly pathogenic strain. This epidemic was particularly difficult for home gardeners and organic producers (4) because such widespread distribution of *P. infestans* was highly unusual for those producers, and, initially, many were ignorant

of late blight. Conventional potato growers were much less seriously affected because they were accustomed to dealing with late blight and more rapidly initiated fungicide sprays.

Knowledge of population structure of *P. infestans* has provided some clarity concerning the development of fungicide resistance in diverse locations. In South Africa, the US-1 clonal lineage is still dominant, and there are both mefenoxam-sensitive and mefenoxam-resistant strains (71). A logical conclusion is that mefenoxam resistance arose in the US-1 population in South Africa and was subsequently selected by use of mefenoxam. In contrast, in the United States, mefenoxam resistance has been associated only with lineages of *P. infestans* that were most likely introduced from Mexico (37, 42), and there seems to be no evidence that mefenoxam resistance in the United States arose de novo in a lineage that had been in the United States for some time.

These migrations and population displacements provide at least two cautionary messages. The first is that it is difficult to define an isolate or a population by its geographic location of collection. For example, isolates found in Ireland in the late twentieth and early twenty-first centuries were almost certainly introduced from Mexico only a few decades earlier. Similarly, US-8 in the United States is clearly recently derived from northwest Mexico (37). Any suggestion that *P. infestans* isolates collected in Ireland in the 1990s or 2000s are somehow Irish or that US-8 is somehow American needs to be qualified to indicate that each is only recently Irish or American. Similarly, newly identified isolates from West Bengal in India (13_A2) were recently introduced. The second cautionary message is that because migrations followed by selection can cause such dramatically rapid population shifts, the characterization of a population in one year may not necessarily be predictive of the population into the future.

## New Understanding: Sexual and Asexual Populations

Analyses with biochemical and molecular markers have led to the conclusion that there are at least two regions globally that are host to residential sexual populations. (The term residential is used here to identify a population of *P. infestans* in which oospores occur commonly in soil and are involved in initiating the local epidemics of late blight.) The first region is the highlands of central Mexico. There have been many studies that document the high genetic and genotypic diversity of *P. infestans* in the highlands of central Mexico and many of these are reviewed in Reference 44. It seems likely that this location is also the center of origin of *P. infestans* (43). The second region is in northern Europe. The very high levels of genotypic diversity in northern Europe (for example, see 6, 72, 73, 80) are consistent with residential sexual populations existing in that region. The most complete picture has been compiled for the Scandinavian countries (reviewed in 88). The impact of the establishment of a residential sexual population in the Scandinavian countries is earlier onset of disease and greater amounts of fungicide used to combat late blight in these countries (46).

Molecular markers have sometimes enabled conclusions that sexual recombination contributes little or nothing to the population diversity in a region even if both mating types are present. There are several potential explanations. First, if individual outbreaks in a field are each caused by a single genotype, then individuals of opposite mating type have little chance to interact, and without physical contact, no sexual recombination occurs. Second, the fecundity of crosses is a function of the parents, and crosses involving some combinations of potential parents do not lead to many oospores. For example, Fay & Fry (24) found that among 35 crosses (A1×A2), half produced few or no oospores and only 3 produced abundant oospores (24). Third, the occurrence of sexual recombination may be so rare that its contribution to population structure is difficult to detect. Fourth, the progeny may be less fit than the parents (66) such that the recombinant population is ephemeral and recombinants are not detected.

Although populations of *P. infestans* remain strongly clonal in the United States, two recombinant populations have been described there. As of 2015, these populations have been ephemeral: After the initial detection, there has not been further production of new recombinant individuals and most strains were not detected subsequently, probably because most of the recombinants were not as fit as the parental genotypes. The first recombinant population was detected in the Columbia Basin of the Pacific Northwest in 1993 (36). The authors of Reference 36 postulated that the parents of this population were US-6 and US-7, and that one of the progeny was US-11 (36), a lineage that has been very troublesome for more than 20 years. However, other progeny of this recombination event have not been detected for many years, and no other potential recombinants have been reported in this general location.

The second recombinant population in the United States was reported recently from the northeastern part of the United States (16). Most isolates were detected in central/western New York State. These isolates were detected in 2010 and 2011, but not in 2012 or 2013. As in the Pacific Northwest in 1993, this population contained diverse individuals in a somewhat localized region and had a great diversity of allele combinations based on analysis of allozymes, mating type, RFLPs, and microsatellites (16). The parents of this population were postulated to be US-22 (A2) and at least two other genotypes. Using a recent protocol that identifies at least 36 mitochondrial haplotypes, these individuals were all determined to have mitochondrial haplotype H-20, the same haplotype as US-22 (16). As with the 1993 population, most progeny in this 2010/2011 population have not been detected since 2011 (16).

These two reports of recombinant populations in the United States demonstrate that sexual reproduction is possible in the United States. Because recombinants have different phenotypes from either parent, and because there is a chance that one of them could become a dominant lineage, it is crucial to determine the phenotypic characteristics of any recombinant individual genotype.

## CAN NEW AND OLD TOOLS RECONCILE DISCORDANT LAB AND FIELD RESULTS?

### Discordance

It is unfortunately not particularly surprising that predictions from the results of lab experiments are not always confirmed in field experiments. This lack of alignment often leads to unpublished (or unpublishable) results. I provide from my lab two examples of discordance between lab and field experiments using new tools (transgenic plants) and old tools (field assay for resistance). I then suggest how a combination of new and old tools might provide potential explanations.

In the first example, my lab group attempted to use field experiments to quantify the enhanced resistance in potatoes achieved by overexpression of PR5 (osmotin) in transgenic plants. The overexpression of osmotin had been reported to delay symptoms of late blight in transgenic plants in growth chamber experiments (62). However, in our field tests with such transgenic plants, we observed no delay in symptom development. Initially, we wondered whether the variance in our field experiments was too large to be able to detect such differences. However, this explanation seems unlikely because in other field experiments we have consistently been able to see rather small differences in resistance among diverse cultivars and segregating populations (23, 25, 77). Thus, there must be a different explanation.

A second example of our inability to confirm lab results in the field was illustrated in a very large experiment (**Figure 2**) that we conducted some years ago using transgenic potatoes with engineered resistance. The construct of interest had enhanced the resistance of plants in lab and

growth chamber studies. Our goal was to quantify that enhancement in the field. There were several treatments: plants with the intact vector, plants with the empty vector, plants with a partial vector, plants with no vector but that had come through the transformation process, and other controls. There were 100 unique transformation events for the vector, 100 transformation events for the empty vector controls, 100 transformation events with a portion of the vector, and more than 40 individuals in each of two other controls. There were also standard cultivar controls, all adding up to 396 treatments. The experimental design was a randomized complete block with three complete blocks. Each of these 396 treatments consisted of plants propagated via cuttings, and plantlets were transplanted to the field in 5-plant plots. We learned that putting potato plants through the transformation process produces plants with detectable diversity, both morphologically and in terms of resistance to late blight. There were some small but statistically significant individual plant differences, but these differences were not associated with treatment. Thus, we concluded that this construct did not lead to resistance in the field (**Figure 2**). Again, the lack of a significant treatment effect was not because of high variance.

## Potential Causes for Discordance

Clearly, there are many differences between field experiments and lab experiments, but in the two cases above, the differences were not due to high variance in the field experiment. Instead, there must be some other differences. Two possibilities are that (*a*) *P. infestans* behaves differently in the field than in the lab and that (*b*) plants may respond differently in the field compared to in the lab. These differences could lead to an interaction that is different in the lab compared to that in the field.

**Is *Phytophthora infestans* growing on an agar medium in pure culture the same as *Phytophthora infestans* growing on a plant in the field?** As measured by at least one characteristic, a sporangium from a leaf lesion is definitely different from a sporangium from culture. That characteristic is the reaction to solar radiation. The difference was detected by chance. In an attempt to determine the effects of solar radiation on sporangial survival, Mizubuti et al. (68) put dry sporangia on a microscope slide and then exposed them to different amounts (durations) of solar radiation. The initial experiments were discouraging, as all sporangia died immediately upon exposure. This experiment was repeated many times with the same discouraging result. The sporangia for these experiments were obtained from a pure culture of *P. infestans* growing on an agar medium. By serendipity (desperate attempts by a graduate student), Mizubuti used sporangia from infected tissue in the field. Much to his relief and surprise, these sporangia survived brief exposures to solar radiation! Using such sporangia Mizubuti learned that sporangia can survive bright sunlight for short periods and can survive indirect sunlight for some hours (68). Upon learning of this difference between sporangia produced on artificial medium in Petri plates and those produced from a lesion, our lab converted to using primarily sporangia from infected leaves (from the lab or the field) for our subsequent experiments.

Subsequently, we learned that the previous history of a strain can have a lingering effect on its phenotype. For example, Childers et al. (10) demonstrated that *P. infestans* exposed to mefenoxam in culture can develop an induced resistance to mefenoxam. The induced resistance persists through several transfers on medium free of mefenoxam (10).

We also learned that sporangia from lesions are generally more aggressive/pathogenic than are sporangia from culture. This is hardly a new discovery; part of the art of plant pathology is to "passage" a pathogen through its host periodically to maintain pathogenicity. In our lab, recent experiments by S.P. Patev (unpublished results) compared disease severity resulting from

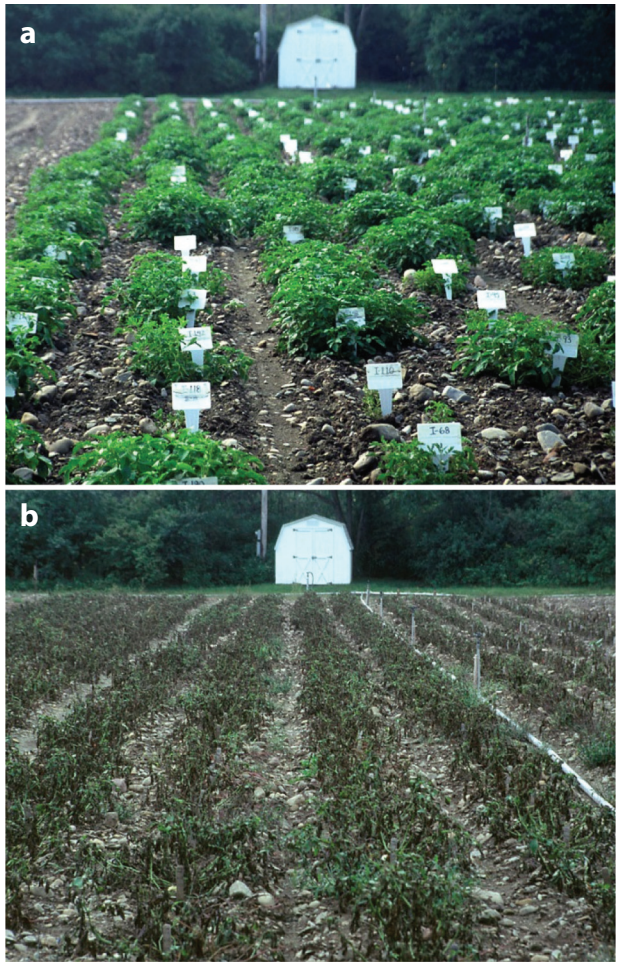


**Figure 2**

Field experiment evaluating the effect of a construct designed to enhance resistance to late blight in transgenic plants. Each individual five-plant plot (observable in panel *a*) consisted of plants from the same transformation event. Morphological diversity is also visible in panel *a*, despite all transformations being conducted in the same potato genotype. (*b*) Although there was some very limited diversity for late blight resistance, most plants (including the nontransformed controls) died similarly rapidly.

inoculation of leaf tissue with sporangia produced in pure culture with disease severity resulting from sporangia obtained from leaf lesions. All comparisons were done with the same number of sporangia of a single clonal lineage. Inoculations were conducted in the field and the lab. In all experiments, sporangia from leaf lesions produced much more severe disease than did sporangia from culture. The differences ranged from 4-fold to >20-fold (S.P. Patev, unpublished results). Additionally, time in pure culture may have an impact. Patev compared sporangia from an isolate that had been in pure culture for approximately one year to sporangia from a culture that had been in pure culture for just several weeks. The sporangia from the strain in pure culture for a year produced less disease than that same number of sporangia from the strain that had been in culture for only a few weeks.

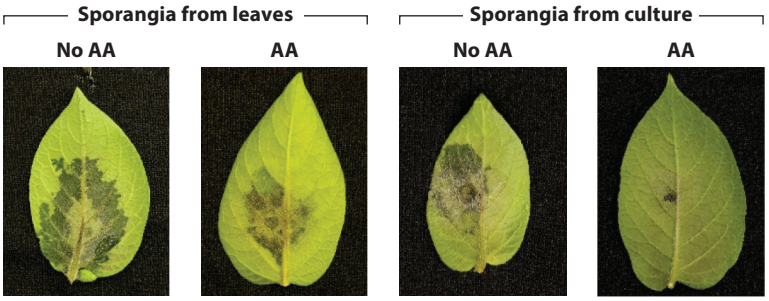


**Figure 3**

Potato leaflets treated or not with arachidonic acid (AA) and inoculated with sporangia from culture or from lesions.

The source of sporangia can cause not only a quantitative difference in disease but also what appears to be a qualitative difference. We discovered this when repeating some experiments concerning the effect of arachidonic acid on resistance enhancement in potato plants. Our group and others had earlier determined that treatment of potato plants with arachidonic acid enhanced the resistance of potatoes to *P. infestans* (64). However, in subsequent experiments, we were baffled by our inability to repeat the experiment and detect the enhanced resistance. We then investigated whether the source of sporangia might explain the difference. In the earlier experiments (64), sporangia were taken from culture. In subsequent experiments, sporangia were taken from leaf lesions. In our troubleshooting experiments, we compared results using sporangia from culture with results using sporangia from a lesion. It turned out that inoculations with the same concentration of sporangia gave different qualitative results depending on the source of the sporangia (**Figure 3**). Sporangia from a Rye B medium detected an effect of arachidonic acid. Sporangia from leaf lesions did not (**Figure 3**). Thus, the source of the pathogen influenced results of experiments evaluating induced resistance. Because the sporangia in the field in a natural epidemic are essentially from lesions on plants, it seems important to use such sporangia in many lab evaluations.

A second factor that might explain some of the lack of concordance between lab and field results is that the plants might respond differently in the field than in the lab or growth chamber. If that is a possibility, it seems that the question in the next section is particularly important.

**Is it possible to gain insight into host responses to pathogens via field studies?** The idea of conducting a field experiment to investigate molecular host-pathogen interactions may seem crazy to some investigators, probably for a variety of good reasons. The lack of available technologies and the inability to control the environment in the field have been significant obstacles. However, new technologies now enable gene expression profiling studies to be conducted in the field, and if all treatments are subject to the same environment, treatment effects might be detectable. Despite these obstacles and driven by our desire to understand the biology of *P. infestans* in the field, we conducted a gene profiling field experiment (**Figure 4**) (7). We compared gene expression in tomato breeding line M82 with that in its near-isogenic introgression line IL6-2 (22). IL6-2 is more resistant to *P. infestans* than is M82 because of an introgression of part of chromosome 6 of *Solanum pennellii* into *Solanum lycopersicum* M82 (77). Our study was done with what is now an older technology, a microarray. Next-generation sequencing should make such studies much more accessible.

We first investigated the potential variance in such an experiment, looking for false positives, false negatives, and inherent volatility. In an analysis of gene expression within each single tomato

**Figure 4**

Field experiment to assess gene profiling in response to infection by *Phytophthora infestans*.

genotype, more than 18,000 transcripts were identified, and with moderately stringent criteria, none would have been identified as differentially expressed (7). Thus, within-field variance seems not to be an insurmountable obstacle to the conduct of gene expression profiling experiments in the field. We next examined whether certain genes in field-grown plants were more likely than other genes to be detected as differentially expressed. In the absence of infection by *P. infestans*, we constructed a list of transcripts that were identified with high variance. Of the 200 most variable transcripts in each tomato genotype, 34 were common to both genotypes, and the most variable of these were genes identified to be involved in biotic or abiotic stress response (7). The six most variable transcripts were catalase and five pathogenesis-related genes (7). There are several potential hypotheses to explain these observations, including the following: (*a*) These genes are responding to some type of pathogenesis; (*b*) these genes are inherently variable and respond to a diversity of stimuli [it is interesting to observe that the response to abiotic and biotic stress can apparently involve many of the same genes (20)]; and (*c*) plants growing in the field are under constant stimulation and the default condition for plants in the field is for these genes to be easily upregulated. A possible implication from this last possibility is that the upregulation of these genes when a plant is challenged in the lab with a pathogen may reflect a response to a general perturbation rather than a specific response to pathogenesis. These results lead to a testable hypothesis: that plants growing in the field are in a constant state of defense.

The next question concerned whether such a field experiment might actually reveal insight into genes that are involved in host resistance to *P. infestans*. The above experiment identified 991 genes that were differentially expressed between the two near-isogenic genotypes. Genes upregulated in IL6-2 and nonresponsive in M82 were targeted for silencing in the lab (7). Sporangia for all inoculations came from leaf lesions. Silencing was successful for two such genes. The first gene was a TIR-NBS-LRR homolog, and when it was silenced in IL6-2, the pathogen grew faster than in the nonsilenced plant (7). There was no effect on pathogen growth rate when this gene was silenced in M82. The second gene was a peroxisomal membrane protein, and when silenced in IL6-2 it tended to increase the pathogen growth rate ($P = 0.066$); again there was no effect on pathogen growth rate when this gene was silenced in M82 (7). Thus, it appeared that at least some genes identified via a field experiment as differentially regulated in these two near-isogenic plants

may have a role in the greater resistance in IL6-2 relative to M82, and it does seem possible to gain some insight into host-pathogen interactions in some types of field studies. It will be interesting to learn whether field experiments might eventually enhance the efficiency of finding genes actually involved in resistance in the field.

## The Enhanced Need for Phenotypic Analysis

The logical final arbiter of many genomics studies is a phenotypic assessment. However, the ability to assess phenotype has lagged woefully behind the wonderful advances in high-throughput genomics. Such genomics studies have led directly to huge data sets that can be analyzed for a diversity of purposes and that have created real excitement. That same excitement needs to be associated with phenotypic studies. I submit that phenotypic studies (in the field) should probably be conducted earlier than is typical in today's (2015) studies. This is because an earlier assessment of phenotype in the field enhances the efficiency of projects designed to understand host-pathogen interactions and host resistance in the field.

An important illustration of the positive interplay between genomic and phenotypic assessment concerns predictions about a resistance gene from *Solanum bulbocastanum* [*RB* (78) = *Rpi-blb1* (84)]. When this resistance was discovered, it appeared to be very broad spectrum and was effective not only against all individuals in local populations in the United States (49, 78) but also against all individuals in a very diverse population in the Toluca Valley in Mexico (78). This resistance gene enabled recognition of (resistance to) *P. infestans* individuals containing the gene *ipiO* (in planta induced) (70), a gene that occurs in many isolates of *P. infestans* (86). For this reason, there was optimism that this gene might not be overcome (lose its efficacy). However, it turns out that there is diversity in this gene family, with the *ipiO* variants being categorized into three classes (I, II, and III) (9). It also turns out that different isolates of *P. infestans* contain different numbers of *ipiO* variants (45), up to 17 variants reported from a single isolate (45). The resistance gene *Rpi-blb1* recognized *ipiO* variants in classes I and II, but not in class III (9). Thus, it was thought that profiling the occurrence of *ipiO* variants in a pathogen population could predict the efficacy of *Rpi-blb1* resistance (9). However, *P. infestans* is a fascinating organism and some isolates carrying *ipiO-1* were found in phenotypic assessments to be unaffected by the resistance conditioned by *Rpi-blb1*. It turned out that these isolates also contained the *ipiO4* variant and IPI-O4 apparently blocked recognition of IPI-O1 (45). Only a phenotypic assessment could have led to this discovery.

The late blight community is beginning to address the genomic basis of important and potentially complex phenotypic traits such as fitness. Phenotypic and genotypic analyses have identified some excellent examples of fit lineages. US-8 in the United States and Canada was very successful from 1994–2009, and 13_A2 in Great Britain was dominant from 2005–2008. Both US-8 and 13_A2 seem to be particularly pathogenic, with characteristics that were strongly selected. For example, when US-8 was first introduced into the United States, metalaxyl was commonly used because it was effective against the then common strains (29); thus, the metalaxyl tolerance in US-8 (42) contributed significantly to its predominance. It was more aggressive on tubers than other lineages (56), and it grew more rapidly in foliage (54). Interestingly, US-8 had many unnecessary virulence factors (e.g., it was unaffected/unrecognized by several of the standard set of resistance genes derived from *Solanum demissum*) (41). Similarly, the 13_A2 strain was particularly fit in the early 2000s in Great Britain. This lineage was first detected in mainland Europe in 2004 (14), and it subsequently has had a local and global impact, causing unexpectedly severe disease in Great Britain from 2005 to 2008 (14) and severe epidemics in China (61) and India (12). In controlled tests, this lineage produced larger lesions more quickly than did the sequenced reference strain T30-4. It also predominated in a field experiment that was inoculated with 13_A2 and four other

strains, and it was able to overcome the resistance in the potato cultivars Stirling and Lady Balfour (14). Because Stirling and Lady Balfour are not widely grown, 13_A2 could also be regarded as having unnecessary virulence.

Genomic analyses of 13_A2 compared with the reference strain T30-4 revealed some fascinating differences (14). There were more candidate RxLR effector genes in 13_A2 than in T30-4; however, these genes were also present in other lineages in Great Britain in various combinations (14). In gene expression assays, there were more candidate RxLR effector genes upregulated in the biotrophic stage of infection by 13_A2 than in infection by T30-4 (14). These candidate effectors represent hypotheses about the genetic basis of relative fitness, and it will be fascinating to learn whether they contribute to the relative fitness of 13_A2. A cautionary note about the role of specific effectors on the fitness of any particular individual of a clonal lineage is that effectors are remarkably mutable, and effectors in one strain of a clonal lineage may differ from effectors in other strains of that lineage (41).

The crucial nature of phenotypic assessment for an accurate understanding of host pathogen interactions in the field is universally recognized, but technological difficulties have been obstacles to the conduct of such studies. By necessity, almost all studies on the interactions between hosts and pathogens have been restricted to lab studies and carefully controlled growth chamber studies. However, new partnerships among investigators and new technologies will enable field assessments of phenotypes earlier in studies on host resistance, pathogenicity, and fitness. The first progress comes with crop plants. Plant breeders have been the first to champion the need for high-throughput phenotyping (3, 13), and it is now becoming possible to achieve high-throughput phenotypic assessment on crop traits. Machines that can monitor many traits as the crops are growing in the field are now being deployed (**http://www.lemnatec.com/news-conferences/article/deep-field-phenotyping-becomes-reality-at-rothamsted-research/**). Hopefully, high-throughput approaches will also be applied to host-pathogen interactions in the field in the near future. My prediction is that an earlier field assessment in studies of host-pathogen interactions will accelerate an accurate understanding of that interaction in the environment of importance, the field.

## TOWARD PRECISION MANAGEMENT?

At the present time successful suppression of the late blight disease requires an integrated approach, mainly with old tools (e.g., sanitation, fungicides). Massive amounts of fungicide are used annually; for example, in the United States alone, more than 2,000 tons of fungicide were used in 2001 (83). Diverse late blight forecasts have been developed over the decades to aid the efficiency of fungicide, but, generally, their adoption has been less than desired by the developers. Fortunately, new tools (improvements in computational capacity to enhance data acquisition and analysis) are presenting some very interesting opportunities for precision management.

### Precision Late Blight Management: A Case Study (BlightPro/USABlight) in the United States

Precision management requires a diversity of old and new tools. One new tool is the dramatic increase in computational capability, which makes possible the acquisition of site-specific weather data and the availability of site-specific weather forecasts. In this case study, weather data from a weather station (on farm or nearest available weather station) are accessible via the Northeast Regional Climate Center (NRCC; **http://www.nrcc.cornell.edu/**) (75). In addition to the observed weather data, a high-resolution weather forecast on a 2.5-km grid is provided by the NRCC.

Thus, observed weather data and forecast weather data for a specific location are available. In this case study, these data are made available via a web-based decision support system (DSS) named BlightPro (75). A user of the system sees observed and forecasted weather data for a location specified by the user. The system is updated several times a day, and these data are used in updated disease forecasts (see below).

Another factor that contributes to precision management is knowledge of whether or not *P. infestans* is in the location of interest. In most locations in the temperate regions (where there is not a residential sexual population), a production field that has late blight in one year does not necessarily have late blight in the subsequent year. This is certainly true in the United States. Despite the sporadic occurrence of late blight in the United States, the potential for this disease to be dramatically destructive causes growers to assume that the pathogen is present, and they typically apply fungicides prophylactically. Knowledge of whether or not late blight is present is very important for two reasons: (*a*) If late blight has been reported close to a given production field (this pathogen can be dispersed in the air for up to several miles), growers need to be very alert and deploy the most effective management technologies, and (*b*) if growers know that late blight has not been reported in their region, they can relax their management efforts by, for example, lengthening the interval between fungicide applications. Thus, knowledge of whether or not late blight has been reported within several miles of any production area is extremely important to precision management of late blight.

A consortium of investigators in the United States has collaborated from 2011 to the present (2015) to share geographic information about outbreaks of late blight. This collaboration was stimulated by the 2009 pandemic and supported by federal grants from 2011–2015 and has been extended into 2017 (USDA AFRI). These collaborators constructed a national website (**http://usablight.org/**) that publishes the county in which late blight had been reported. Persons can request to receive reports of new occurrences of late blight. Reports by nonconsortium members are validated by consortium members. Since 2011, use of the website increased dramatically each year; in 2014 alone, there were more than 25,000 visits to the website, which identified 349 active sites, and more than 16,000 alerts were distributed to interested persons (Ryan Boyles, personal communication).

It is also important to know the phenotypic characteristics of the pathogen that caused the nearby outbreak. Collaborators and others submitted samples to a central lab for genotype identification. Recently developed microsatellite markers (59) were used to identify the clonal lineage of *P. infestans* in each sample that was submitted. The specimens were sent mostly via overnight courier, and in the vast majority of cases the results were returned to the submitter within one or two days of receipt. This information was valuable to the submitter because each clonal lineage had reasonably consistent and unique fungicide resistance and host preference characteristics, which could help growers develop their management plans (see 28).

The population of *P. infestans* in the United States continues to be dominated by relatively few clonal lineages (35, 51). The most recent dominant strains are US-8, US-11, US-22, US-23, and US-24 (28). Individuals within a lineage are similar to each other in most characteristics. However, there can be important differences among lineages (28). For example, the most common lineages differ in terms of their response to mefenoxam, the most effective oomycete fungicide against sensitive strains (29). Mefenoxam is ineffective against resistant strains (42). From the mid-1990s to 2009, most clonal lineages in the United States were resistant to mefenoxam (28), so growers did not use mefenoxam during that time to manage late blight. However, more recent dominant lineages have been largely sensitive to mefenoxam (65, 74). These lineages are currently incompatible with tomatoes carrying the *Ph-2* and *Ph-3* genes for resistance; thus, cultivars with these genes should be resistant. However, if a new lineage were to appear, its reaction to these

resistance genes should be investigated. Only monitoring will enable such investigation to occur. Thus, knowledge of the lineage in a particular area provides crucially important information necessary to select the most effective management strategy. Eventually, molecular markers for specific effectors and fungicide resistance are likely to replace the need to identify clonal lineage.

A platform to integrate the diverse components in a convenient manner is very helpful. The DSS BlightPro, available on the web, integrates much information useful to the management of late blight. For example, in addition to using the site-specific weather data and weather forecasts, it incorporates information about the pathogen, the host, and management technologies. If a user of the DSS is aware that a particular lineage has been found nearby (via **http://usablight.org**), s/he can find descriptions of the lineages on the DSS. The impact of weather on late blight development is described by either of two late blight forecasting models: Blitecast (55) or Simcast (27). These models use weather data and forecasts for the location chosen by the user. Both forecasting models use weather forecasts (available in the DSS) to make disease forecast predictions several days into the future. Simcast, however, also uses information about host resistance effects and fungicide effects (27). The relative resistances of most of the popular potato cultivars (and some of the many tomato cultivars) in the United States, as well as characteristics of most of the common fungicides, are also provided in the system (75). Finally, the DSS also hosts a complex mechanistic simulator of the late blight disease (2), which can be used to project disease progress and fungicide residue into the future.

It seems likely that the DSS in combination with the ground truth of knowledge of outbreaks of late blight and the pathogenicity characteristics of the lineage that causes the outbreak will enable a more precise approach to disease management. Both initial field tests and a series of simulation analyses suggest that use of the DSS can improve the efficiency and efficacy of late blight management (76). When using Simcast as the forecast tool on BlightPro in field experiments, the effects of host resistance generally resulted in fewer fungicide applications but with equivalent disease suppression compared with the effects of a standard weekly application schedule (76). Simulation experiments provided a more thorough evaluation, utilizing 14 years of weather data from 59 locations in diverse states in the United States (for a total of >750 simulation experiments). Again, the use of host resistance improved the efficiency and efficacy of disease suppression. When weather was unfavorable for disease, the DSS recommended fewer fungicide applications and yet there was no loss of disease suppression compared to a standard weekly schedule. When the weather was very favorable for disease, the DSS recommended more fungicide applications, which provided better disease suppression (76).

## WHAT IS NEXT?

Given the current capabilities to acquire and process data and the recent dramatically increased understanding of *P. infestans* (from the molecular to the population level), it is hard to be anything other than very optimistic about our future ability to improve late blight management, particularly in locations with simple clonal populations. In the near future, we are likely to have the following:

- Molecular tools for diagnostics. These will enable predictions of important phenotypic traits in the pathogen, such as fungicide sensitivity and R-gene interaction (and perhaps even predictions of aggressiveness and fitness).
- New methods (high throughput?) for sampling and assessing populations. These will enable rapid application of the molecular diagnostics. For example, investigators are currently considering the construction of mobile sensing devices that might indicate whether *P. infestans* is in a location. Detection might be based on sporangia in the air or based on chemicals associated with *P. infestans.* Detection devices could be mounted on tractors (or drones) and

linked with diagnostics for diverse molecular targets that are predictive of the important phenotype.

- High-throughput phenotyping technologies. These will be developed and applied to host-pathogen interaction studies in the field and will inform our understanding of plant resistance, pathogen aggressiveness, and disease management.
- Expansion of disease forecasts to include variance in pathogen populations to diverse environmental factors. Population studies have clearly indicated that there can be diverse responses to environmental factors among individuals in a population. If the phenotypic characteristics of a pathogen are known, disease forecasts will be constructed to become responsive to that new information.
- Data-processing platforms that will integrate important diverse data in near real-time. Prototypes have already been developed, and their utility in decision making has been demonstrated. Given the available models and computational capacity, it will likely become possible to identify optimal solutions to resource allocation questions in near real-time.
- Precision management software (including new types of forecasts). These will be directed at specific fields but will also be informed by information from adjacent fields.
- Crowdsourcing of important information about late blight occurrence. The initial enthusiasm for the USABlight website illustrates that gardeners are eager to share information. Such information will improve dramatically our understanding of the spatial distribution of late blight in the very near future.

## DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

## ACKNOWLEDGMENTS

I wish to thank Dani Shtienberg for particularly helpful discussion of this review. Silvia Restrepo, Giovanna Danies, Hilary Mayton, and Ian Small provided helpful comments on drafts of this manuscript. Thanks also go to Kevin Myers, who provided many genotypic analyses of isolates. I also wish to thank these individuals and the more than 50 students and postdoctoral scientists with whom I have been privileged to work over the past 40 years, and who have provided many of the data reported in this review. Construction and maintenance of the USABlight site and recent improvements of BlightPro were made possible by a grant from the Agriculture and Food Research Initiative Competitive Grants Program (Grant 2011–68004-30154) of the USDA and by NIFA Grant (Hatch/Smith Lever) 10000830, project NYC-153421.

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