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EPIDEMIOLOGY: A Science of Patterns

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■ **Abstract** During the twentieth century disease detectives progressed by jagged leaps in understanding patterns of plant disease. With ladders, airplanes, and automatic traps they observed airborne spores, and with meteorological theory they explained takeoff, flight, and landing. They analyzed the grand, logistic rise of epidemics and the roles of horizontal versus vertical resistance. From early experiments on the details of life cycles and weather, they simulated epidemics with new computers. Early in the century they revealed genetic diversity with differential varieties and late in the century with differential fungicides and DNA. They learned the interplay of pest, photosynthesis, and supply and demand to reckon loss. Integrating observations of pest, host, losses, and weather, they placed winning short-term bets for farmer and environment on whether to spray. In the twenty-first century, their goal can be analyses so sound that the world can securely place winning long-term bets.

CONTENTS

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INTRODUCTION

Patterns

Epidemiologists study the patterns of disease on a map, in time or in a population. Where did they begin the twentieth century, what did they learn during 100 years, and where would they be smart to work during the twenty-first century?

Before the twentieth century, epidemiologists had established themselves as detectives of patterns. Before 1800, a traveler saw the villainy of barberry in patterns of wheat rust around them (22). In 1854 before the cholera pathogen was discovered, Dr. Snow detected in the disease pattern around London's Broad Street pump that cholera was waterborne (73). Near 2000 AD, plant epidemiologists are sleuthing out the origin of cypress canker (31).

In 1927, WH Frost, the dean of American epidemiologists at the time, wrote, "The nature and spread of a disease may often be established quite firmly by circumstantial evidence well in advance of experimental confirmation" (76). Epidemiologists are detectives.

They are also judges. In 1927, Frost also wrote, "Moreover, many problems of disease transmission which are highly important from the standpoint of prevention, are such that can be solved only by [epidemiology]." Without epidemiology encompassing populations in the real world, people could not judge which touted cause, medicine, or policy lived up to promises resting on correlation, experiment, or testimonial.

Detecting and judging, epidemiologists concentrate more on the whole than the parts. At the end of the twentieth century, preoccupation with ecosystems perceived as greater than the sum of their parts inclines science to secondary wholes like epidemics and somewhat less to primary parts like fungi. Watching a disease expand in a field or rise under the macroscope of a curve in Cartesian coordinates, they can perceive an epidemic as an entity without dissecting it into environment, host, and pathogen. We perceive elephants, potatoes, and wheat without dissecting them into their molecules, so why not epidemics, too? "The

whole is more than the sum of its parts" is the core of the old Gestalt theory of perception. The theory holds that a pattern may have characteristics not inherent in the elements that made it.

At the end of the century the macroscopic Gestalt or holistic view generates excitement. To judge whether hypotheses about the parts and their management matter in the wholes of epidemics, however, epidemiologists cannot be content with enjoying macroscopic views. Detectives delve into the primary elements that create epidemics so they can generalize or model other wholes. Thus epidemiologists scrutinize patterns of disease under a macroscope. They detect what causes disease and must judge what effectively discourages disease in the big world.

Plant Epidemiology Compared to Medical

Long ago the epidemiologists studying plants stopped distinguishing their branch as *epiphytology*. Comparison with its cousin medical epidemiology highlights the present character of plant epidemiology. A menu (76) of medical epidemiology encompasses lung cancer, heart disease, environmental hazards, medicines that backfire, and screening seemingly healthy people. Medical epidemiology boasts about *disease detectives*. A menu (11) of plant epidemiology encompasses monitoring, experiments, loss assessment, forecasting, and analysis and modeling of disease progress and maps. Other menus for plant epidemiology would add resistant varieties. While medical epidemiologists are proud to be disease detectives, plant epidemiologists are proud to manage disease with minimal environmental impact.

Compared to medical epidemiology, plant epidemiology attends relatively less to noninfectious disease and to detecting such subtleties as pollutant traces that may cause disease. On the other hand, the comparison spotlights plant epidemiology's emphasis on managing disease with little chemical control. Briefly, medical epidemiology tries to find the cause of death that eventually comes despite the defeat of hunger and infectious disease. Plant epidemiology, on the other hand, tries to manage infectious disease with less. Although medical and plant epidemiology both study patterns of disease, at the end of the twentieth century they differ. Their differences may be rooted, however, in human health. One strives to postpone human death, while the other strives to control plant disease without residues that might hasten human death.

State in 1900

At the starting line for our review, 1900, Pasteur had saved a boy from rabies only 15 years before, and Koch was still at work. In plant epidemiology, the Irish famine, Reverend Berkeley, and Anton deBary were closer in time than the Dutch elm epidemic and quinone and dithiocarbamate fungicides are today.

Ward's (87) *Disease in Plants*, published in 1900, shows knowledge of plant epidemics right on the starting line. Ward devoted two chapters to epidemics. He understood the hazard of genetic uniformity and of a pathogen's variability and adaptation to resistant varieties. He wrote, "No disease can be efficiently caused

by an organism alone," and, "Any pest may become epidemic if the conditions favour it." On the other hand, when Ward came to the spread of epidemics, he said nothing about travel on the wind.

To review the century of epidemiology since, we have far ampler resources than two chapters. The *Annual Review of Phytopathology* has published accounts, and Zadoks & Schein (91) and Campbell & Madden (11) wrote entire texts. Large (53) wrote vivid histories of epidemics and the misery in their wake.

Watching scientists, a spectator might think they steadily pushed back the frontiers of knowledge, day after day. The scientists, however, know that their understanding stalls, months at a time, only to jump ahead. As a reminder of the way understanding really changes, Figure 1 shows progress by jagged leaps (see color plate). While the time line organizes the jumps in the chronological order that discoverers had to travel, the wisdom of hindsight allows us to arrange them by subject from measurement to management. As we proceed through the subjects, we generally confine our examples to fungal diseases of foliage.

MEASURING DISEASE

An epidemic may be a pachyderm so different from the fleas of endemic diseases that one can follow the Gestalt habit and say *elephant* without weighing it. Still, as Lord Kelvin said, when you cannot measure what you are speaking about and express it in numbers your knowledge is of a meager and unsatisfactory kind. The dependence on numbers of breeding resistant varieties and of evaluating fungicides evoked measurement (39). Chester (14) wrote that Yachevski began modern plant-disease-appraisal in 1929, and a 1953 survey of potato scab provided clues to resistant varieties (55). Numbers underlie all economic analysis of control (13).

Because countless lesions may overwhelm our eyes and because we perceive comparatives better than absolutes, Cobb (16) diagrammed just five standard areas to compare with lesions. In 1922, Stakman & Levine differentiated physiologic races along photographic scales of rusted leaves (74). Equating small scab spots on about a quarter of the apples on five branches with 0.5% scab exemplifies saving time to get the work done (55).

The Horsfall/Barratt scale that "accelerated data taking to a usable level" rests on human perception rather than on particular diseases and proved more general (38). Dependence of visual acuity on the logarithm of stimulus, first from 0 to 50% diseased and then from 50 to 0% healthy, set their scale.

Accelerating measurement even more, a Californian tested disease survey from the air (17), and a satellite spied differences in wheat rust across the Indian/Pakistan border (63).

If multiple infections occur, the number of lesions need not equal the number of propagules, even the number of successful ones. So, when Gregory (33) studied spore dispersal in the 1940s, he did not equate their footprints of lesions with unseen spore landings. Instead he translated them into larger numbers with the multiple infection transformation, i.e. Poisson frequency distribution.

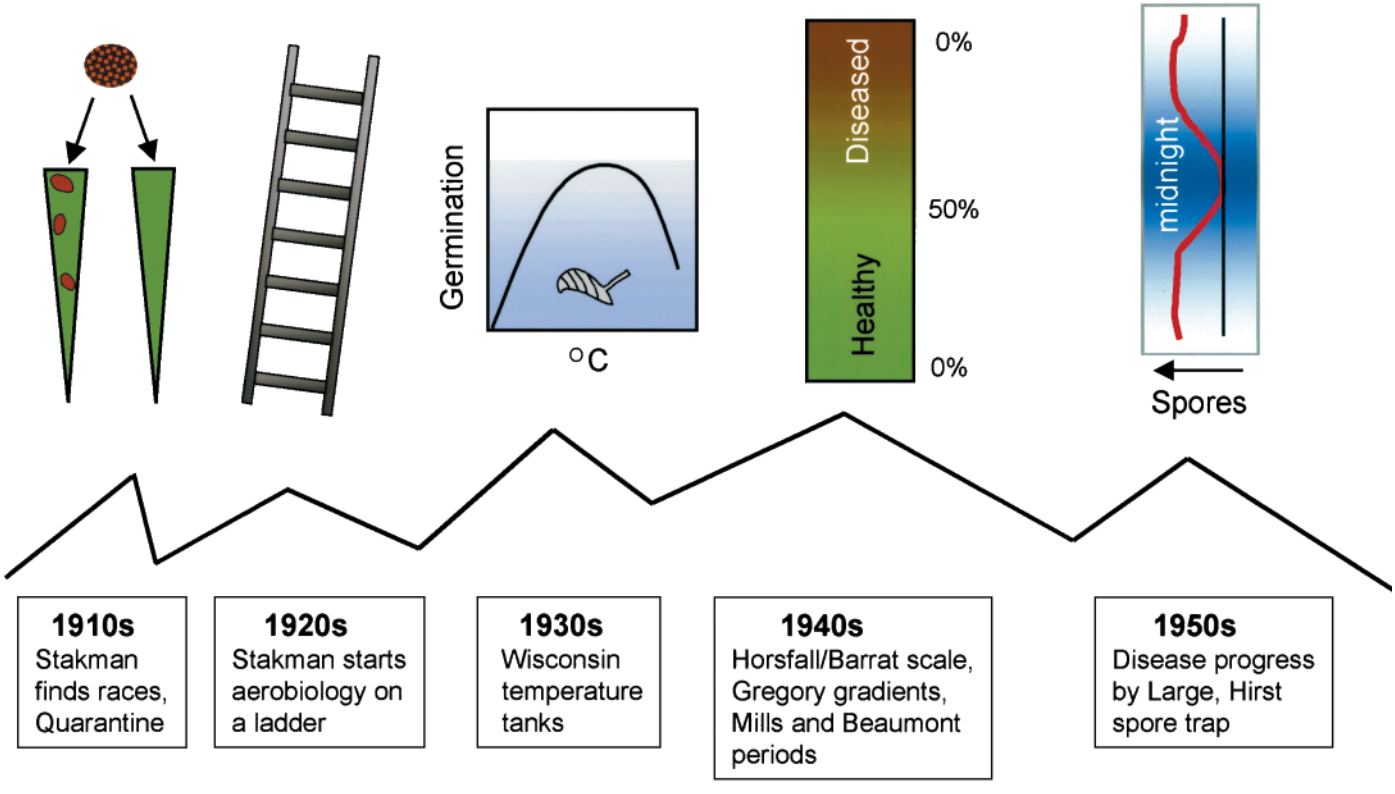

Figure 1a

Figure 1a b (next page) A time line of the jumps in epidemiology during the twentieth century.

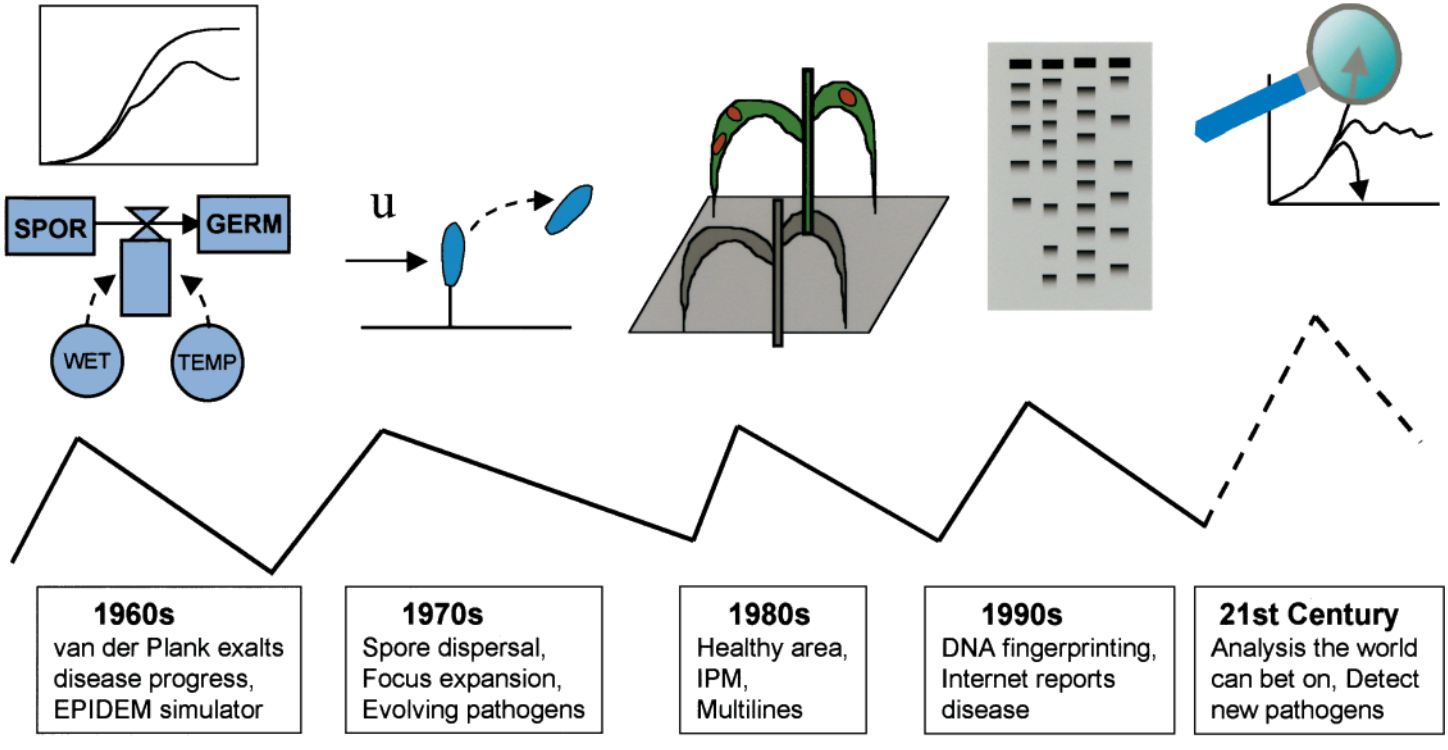

Figure 1b

Similarly, if hosts have more than one lesion, the number of hosts diseased will be less than the number of lesions. Practically, of course, the two numbers may climb together until, say, half the hosts are infected (42). Nevertheless, few could have been surprised that several times as many leaves usually remain healthy than expected from the number of lesions, even after the multiple infection transformation, which rests on an assumption of randomness. The number of diseased leaves usually rises more slowly than if additional lesions were scattered at random and instead rises at a slower rate described by a *contagious* distribution (84). Near the end of the century, several epidemiologists were exploring patterns of disease for evidence of contagion or aggregation (25, 30, 41).

By the end of the century, sophisticated epidemiologists knew how to relate the number of spores, lesions, and diseased hosts. They knew the best method worked within their available time and led directly to their goal. They chose different methods according to whether they were detecting causes, breeding for resistance, choosing a fungicide, measuring dispersion or assessing the farmer's loss to disease—which we return to later.

IGNITING EPIDEMICS

Despite the glamour of burgeoning microbiology, epidemiologists of plants entered the twentieth century remembering that host, environment, and pathogen must be in conjunction to ignite an epidemic. Nevertheless, we begin with the arrival of pathogens.

New Pathogens

For decades before 1900 humanity had suffered plagues that would have softened a Pharaoh's heart. "They came in the wake of the industrial revolution, with the specialized cultivations, and with the growth of maritime trade. Some were ancient, some were new, they were no mere visitations; where they were introduced they came to stay" (53). Just before the twentieth century, coffee rust erupted in Ceylon, introducing Ward to epidemiology and assuring epidemiology would appear in his 1900 text. After 1900, fresh examples reminded people how new pathogens ignite dangerous epidemics. At the opening of the century, chestnut blight pathogen arrived in the New York Zoological Park to begin its sweep of America. A third of the way through the century, logs for furniture brought the Dutch elm disease pathogen across the Atlantic. In 1970, Southern corn leaf blight, which had first appeared in the Philippines, swept across America. And at the end of the century, cypress canker is a pandemic in progress, centered on the Mediterranean.

Quarantines

Blaming *maritime trade* for spreading pathogens adds man to the disease triangle of pest, host, and environment to make a pyramid (91). Blaming trade also evokes quarantines to halt new pathogens at the border. A chronology of quarantines

during the first third of the century showed California struggling alone in the United States until a federal act in 1912. When California queried the efficacy and economic effects of plant quarantines in 1933, the cheap prices for consumers from bumper crops versus high prices for some farmers from scarce crops (a subject we shall return to) rendered answers equivocal (72). The list of pathogens invading despite quarantines, notably the Dutch elm disease pathogen sneaking through a loophole by riding dead logs rather than quarantined trees, undoubtedly makes the inconvenience of quarantines harder to tolerate (85). The overwhelming volume of present trade dims hope that quarantines will catch new invaders and makes the inconvenience still harder to bear. We expect invaders will start future epidemics.

Aerobiology

Although Ward omitted aerial dispersal from his 1900 text, epidemiologists soon found pathogens could fly over quarantines. By 1918, Ward's student Freeman had sent his student Stakman up a water tower with greased slides to capture rust spores in Minnesota air. By 1921, spores had been caught on mountain tops and from airplanes, hinting that winds could blow spores far as well as high along a "*Puccinia* pathway" from Texas, through the Great Plains, to Minnesota (15). Wind apparently also carries stem rust northward from the Nilgiri hills to central India along another *Puccinia* pathway (64).

Although finding pathogens in the air tempted epidemiologists to conclude that invaders from afar were starting epidemics, it was also possible that the airborne spores came from nearby with less dilution in the atmosphere. In 1967, however, few could doubt that the clouds of spores Hirst, Stedman & Hurst flew into and out of across the North Sea proved dispersal for hundreds of kilometers was possible (36).

To start an epidemic, however, invaders must not only fly. They must arrive alive. During flight, extreme temperatures and humidity can kill them. Even more dramatically, ultraviolet radiation can kill invaders, especially hyaline downy mildew spores (68).

Invaders from afar suffer both more exposure and more dilution than ones from nearby. So, the possibility of distant dispersal does not settle the probability that invaders from afar rather than from nearby or invaders carried by man ignited a particular outbreak. By 1982, the need to know paths of radioactive particles plus improving computer technology and meteorology encouraged computing of aerial trajectories. Accordingly, when tobacco blue mold reappeared in Connecticut after a long absence, probabilities of distant versus local aerial transport or even humans' introducing the pathogen could be weighed (6).

Inoculum potential, defined a half-century before by Horsfall (37), anticipated the quantitative view implicit in calculating probabilities. Although he found a mild case of infection possible when the mass and virulence of inoculum were low, he found severe infection when they were high. Going beyond observing the mere absence versus presence of a pathogen, he captured the greater danger of a greater mass and virulence in the illuminating phrase *inoculum potential*.

WEATHER TO ENCOURAGE EPIDEMICS

Mindfulness of the exposure to weather of pathogens flying and landing outdoors caused environmental experiments to figure more prominently in plant than in medical epidemiology. Besides massive numbers, invaders' success outdoors hinges on survival and multiplication, which depends heavily on weather. The clear dependence of epidemics on weather caused Stephen Hales in the eighteenth century to attribute hop mildew to wet weather, Unger in 1807 to designate the pathogen of wheat bunt as only "la cause immediate," and Ward in 1890 to emphasize cool, wet weather as predisposing plants to infection (1).

Despite the importance of weather, Wisconsin epidemiologists early in the twentieth century wrote, "Practically all of our exact data in plant pathology deal with the causal factor, the parasite, and such ideas as we have concerning the relations of environment, the conditioning factors, are general and vague." Wisconsin pathologists (46, 48) were in the vanguard of epidemiologists experimenting to learn how the weather elements affected plant pathogens. Their temperature tank controlling the temperature of soil cans and an inoculation chamber exemplify experiments with weather during much of the century. They showed whether more or less root disease or successful inoculation followed warmer or wetter versus cooler or drier. They explained, for example, the daily increase in apple scab lesions in terms of daily maximum and minimum temperature and rainfall. Experiments showing a couple of degrees Celsius warmer or couple of hours less moisture made the difference between no and many infections justified disease forecasts from simple rules about temperature and humidity.They explained how small environmental differences encouraged epidemics.

Experiments with each step in the fungal life cycle carried understanding into the physiology of pathogens. Crosier (19) explored how controlled temperature and humidity affected stages of a classic subject of epidemiology, *Phytophthora infestans*. His graphs showed that temperature and humidity set the course of formation of sporangia and their mortality or germination directly or indirectly. His graphs showed the motility of the consequent zoospores, penetration of the host, incubation and production of lesions. Crosier's 40-page *Memoir* exemplifies, as do the 144- and 104-page *Wisconsin Bulletins*, the sweeping but thorough reports of the era. When speedy computing arrived a human generation later, these comprehensive and thorough reports were nuts and bolts waiting for computer programmers to assemble into mathematical simulators of pathogen life cycles in varying weather.

SPREADING WITHIN A LOCALITY

Gradients and Traps

Spread within a locality and repeated infection expand a beachhead established by initial inoculum and favorable weather into an epidemic. In the middle of the century, the Rothamsted Experimental Station propelled understanding. Although

epidemiologists knew disease fell away around foci, Gregory (32) (with help from his wife Margaret, a mathematician) explained them. After transforming lesions into spore arrivals with the multiple infection transformation, he analyzed spore dispersal with the physics about diffusion of war gases. Gregory's work inspired great advances to follow.

A spore trap was Rothamsted's second contribution. To the middle of the twentieth century epidemiologists trapped spores in the laborious way Pasteur had used in the middle of the nineteenth century. So the hour-by-hour record of any visibly distinct spores in a volume of air by Hirst's (35) unattended and relatively simple instrument revolutionized aerobiology. It revealed how weather affected spore take-off. The succeeding, smaller and cheaper rotorod sampler (66) measured spore concentrations vertically and horizontally, grist for the mill built by Gregory's theory.

More often than not, disease begins in foci. It begins in spots because pathogens overwinter in spots or arrive sporadically. Or, favorable environments are patchy in a field. Foci often appear first low in the crop canopy and only later spread upward and outward. Low in the canopy, slow winds and little turbulence hinder spore take-off and flight. Although the center of spore production does rise in a canopy as disease intensifies, that comes after spores spread from their initial, low positions.

Take-Off

In the first half of the century, AHR Buller and CT Ingold analyzed the fascinating ejection of ascospores (34), but many pathogens do not help their spores to take off. Because they are often firmly attached to their sporophores, detaching each species of spores requires a threshold of force and so unique thresholds of wind speed to strike them directly. The boundary layer of slow air around leaves within the canopy, however, seemed to leave spores immobilized. Epidemiologists puzzled how spores could ever escape the calm of their initial beachhead low in the canopy. The solution to the puzzle came with the observation that gusts within a canopy sweep away the boundary layer, admit the threshold wind to strike the spores, and carry them into the air (5).

Dilution and Deposition

After spores escape, the disease they spread typically diminishes rapidly along a gradient. Competition between deposition and dilution determines the shape of the disease gradient. While the airborne spores are within the canopy, deposition depletes their concentration exponentially in proportion to their concentration in the same way a column of liquid dims light passing through it. After most of the spores escape from the canopy, however, it is dilution in the air that lessens their concentration much as light dims with distance from the source. Although the difference between gradients where deposition prevails over dilution is small near the

source, it grows great with distance where the difference between the exponential and power becomes the difference between inconsequential and considerable infection.

When spores are detached from lesions deep in the canopy, few may escape the trammeling foliage, causing a consequent sharp, exponential disappearance. As many as half, however, can fly above the canopy within only a few meters (4). In the free air above the canopy more escape deposition and dilution prevails, making spore concentration decrease as a power of the distance. So by the end of century, epidemiologists had the sophistication to view dispersal as a compound of deposition and exponential decrease prevailing near the source and dilution and power law prevailing afar.

In addition to viewing an epidemic spreading along a gradient, epidemiologists also viewed it as a wave advancing along a front (61). Where spore concentrations decrease exponentially, disease fronts can travel steadily (78). Near a source, deposition can cause an exponential decrease and a disease front. Dispersal by splashing rain favors exponential dispersal (26). Where dilution and the power law prevail, an isopath of, say, 10% diseased moves faster and faster out from the source, especially when the pathogen multiplies rapidly (24, 44). Even in this case, washing rain or spores dying in proportion to their numbers (68) can nevertheless decrease disease exponentially and cause a wave front.

Where the locality or field observed is very large and deposition prevails, secondary infection and repeated spread can develop a front with a steep gradient (90). Observing a small or medium field, however, the epidemiologist will see what Gregory (32) saw: Secondary spread makes the focus indistinct and gradients flatter.

To infect, a spore must land. Gregory (34) added an encore to his great contributions by showing the speeds of airborne spores and dimensions of leaf or stem determine whether spores settle, float by, or strike and stick. Settling, the sedimentation thoroughly studied in the first half of the century, dominates in a canopy, except near the top (59). A new microscope, the scanning electron, revealed the germ tubes of landed spores seeking open stomata (69).

In 1900, aerial dispersal did not rate mention in Ward's text, but during the first half of the century, aerobiologists observed spores flying high. During the second half, epidemiologists with better instruments to measure spore concentration in the air and with meteorological theory came to understand the take-off, flight, and landing of spores.

PROGRESS OF EPIDEMICS WITH TIME

Bewildering Patterns

With time, dispersal piled on top of dispersal and multiplication after multiplication along the gradients during weather ranging from brisk, dry wind to splashing rain combined to spread a pathogen across space. While drawing kaleidoscopic patterns

in space, the pathogen also draws bewildering patterns of disease rising and ebbing with time.

To resolve the bewilderment, Kranz (50) compared the entire progress of outbreaks during a two-year study of 59 host/pathogen combinations, searching for a simplifying taxonomy. The patterns of rise and ebb were stubborn, allowing limited simplification and frustrating the search for linear transformations.

Elegance in the Logistic Curve

Van der Plank, however, persisted in focusing on only rising disease and choosing the simplest model of an exponential rise to a limit, the logistic model. This South African's ideas gained an international audience in a chapter of an American book. His transformation of epidemiology, however, came with his own book (80), which he generously inscribed, "To JG Horsfall, who with AE Dimond started this in July 1957."

The transformation was not wrought by the logistic equation, which was old. Verhulst had introduced it in the nineteenth century and, and during the 1920s, students of population had employed it enthusiastically. In 1945, Large (54) had already justified fitting an empirical equation to disease progress solely because its numbers practically followed the logistic. Moreover, decades later van der Plank's admirers (92) concluded, "Logistic growth has proven the exception rather than the rule."

Van der Plank worked his transformation by going beyond *fitting* the logistic curve to disease progress. He employed it to reason how infection rate, latent period, sanitation, and fungicides affected epidemics. As an encore, he introduced the concepts of vertical resistance, almost immunity, against some races of a pathogen, versus horizontal resistance that slows the rise of all races. As an epidemiologist van der Plank interpreted the two resistances in terms of the logistic model: Vertical resistance lowered the initial infection, but horizontal conferred the more enduring advantage of slower infection rate.

Still, in 1936 Fracker (28) had already analyzed the effect of sanitation on rate of infection with the logistic. (Parenthetically, we note Fracker also employed a multiple infection transformation.) So, the question remains, "How could van der Plank transform epidemiology in the second half of the century with a well-traveled model?" The reason was concatenation. His book combined a practical recipe for fitting the model with a demonstration of its use to interpret progress curves in familiar pathological measures like sanitation. The times were ripe: 1963 saw both publication of his book and in Pau, France, the first international workshop on epidemiology (see Figure 2).

By combining the logistic model with the concepts of vertical and horizontal resistance, however, van der Plank made his most brilliant stroke. His names for the two types of resistance soon peppered reviews and indices (9, 40). When the pathogen of Southern corn leaf blight exploited the vulnerability of the homogeneous American crop in 1970, van der Plank's conception of exponential disease

Figure 2 Many cited in the review of twentieth-century plant epidemiology attended the NATO Advanced Study Institute at Pau, France, 1963. From left to right. Front row: PMA Bourke, Mme. Czuti, PR Miller, CT Ingold, AJP Oort, Mme. des Tombe, RD Schein, JM Hirst, JE van der Plank, MV Carter. Middle row: EB Cowling, M Urbain, RA Hyre, J Ponchet, JR Wallin, E Forsund, RV Bega, FA Wood, HT Cook, H Schrodter, LP Smith, PE Waggoner, Mme. JC Zadoks, IF Storey, JC Zadoks, D Lapwood, R Corbez, RW Gloyne, Assistant of M Urbain. Back row: RT Burchill, JA Snow, GA de Weille, EP van Arsdel, CE Yarwood, SM Pady, J Rotem, J Palti, TF Preece, J Ullrich, H Bortels.

progress and taming it with general resistance was at hand to explain what went wrong and what to do (18).

Details with Computer Models

The times were also ripe for another step in understanding disease progress. Although the logistic model helped reason about steady factors like resistance, it remained a Procrustean bed that cut away inconvenient feet like the susceptibility to daily weather of different stages in the pathogen's life cycle. Abundant observations such as Keitt and Jones made of the apple scab pathogen and Crosier made of the late blight pathogen, of course, showed that inconvenient feet as numerous as a millipede's hastened or halted epidemics. Nevertheless, analytical models like the logistic could not accommodate so many feet and computation was too tedious. High-speed computers changed the times and put the abundant observations to work in mathematical simulators of the flow charts of pathogen cycles. In 1968, Crosier's 34-year-old curves supported the first simulator. In 1969, the composition of the second simulator, however, evoked new experiments by revealing gaps in knowledge about weather and a life cycle (83). Still another simulator showed how its flow chart could specify swift laboratory experiments on the stages of the new pathogen of Southern corn leaf blight. Assembling new experiments in a simulator could anticipate the progress of a new disease long before history yielded experience in the field (71). Other notable simulators were composed in Germany [(EPIVEN of apple scab and EPIGRAM of barley powdery (2, 51)] and in the Netherlands (EPIMUL) to demonstrate the spread of a disease and effects of mosaics of resistance and susceptibility (47).

Because analytical models link cause and effect elegantly, complex computer simulators did not put them out of work. Analytical models excel in showing the logical outcomes of competition and the relative fitness of pathogens and of growth of host and pathogen (45).

By the end of the century, epidemiologists could combine their understanding of the effect of weather on stages in the pathogen cycle and aerial dispersal in numerical models of disease progress and use analytical models to apply the concepts of vertical and horizontal resistance.

MATCHING PATHOGEN AND HOST GENES

To actualize the epidemics simulated for invading pathogens and ensuing weather, the genetic patterns of pathogen and host must match. "For each gene conditioning resistance in the host there is a specific gene conditioning pathogenicity in the parasite" (27). New resistance genes in a host or a new fungicide can defeat the annual arrival of an old pathogen. A shifty pathogen can, however, evolve diverse genes to defeat the resistance gene or overwhelm the fungicide, igniting an epidemic. Seeing races evolve to attack resistant varieties early in the century and other races overcome a fungicide late in the century, epidemiologists learned

about the diversity of population genetics. Beyond patterns of disease across space and time, they studied patterns of genetic diversity in populations.

Diversity Disclosed

Blount's breeding of rust-resistant wheat in Colorado in the 1880s seems to have set off the explosion of breeding for resistance that mined diversity to transform disease control and epidemiology. Saunders' 1904 selection of Marquis wheat, Biffen's 1904 demonstration that resistance was a Mendelian character and Orton's and Bolley's breeding resistance in more crops began the new century with a bang.

The resistant varieties promptly exposed pathogen diversity. Near 1900, Eriksson discovered that seemingly homogeneous *Puccinia graminis* actually encompassed several *formae speciales* (*f. sp.*) that infected barley, oats, rye, and wheat differentially. Soon Stakman found that each *f. sp.* in turn encompasses subdivisions eventually called races. While teaching household bacteriology to home economics students, he and Piemeisel inoculated thousands of plants. Tables running on for pages in their report showed diverse pathogenicity to grasses within f. sp. *Puccinia graminis tritici* (75).

In the background of their report, soldiers in the trenches of the Great War drove up demand and price for wheat, but rusted American wheat fields produced less, not more (Figure 3, see color plate). And in the foreground, Stakman and Piemeisel presented the world with a 66-page "real barnburner" (15).

Although shellshock from trench warfare ended Piemeisel's career, Stakman and a new colleague soon produced the system of 12 differential hosts that became the standard for identifying diverse races within *Puccinia graminis* f. sp. *tritici* (74). By 1922, they reported the taxonomic characteristics of 37 but added, "More forms could be recognized if the proper combination of differential hosts were employed." Stakman also took up barberry eradication, which would affect rust diversity. About to launch the campaign, he "Went back home and had many sleepless nights because we didn't know enough to tell exactly how much good barberry eradication could do."

Fortunately, an ally had read of a pattern in a wheat field on Long Island about 1810, "On the southern limit of this field grew a single barberry bush. The southern winds prevailing at the season in which this bush was in bloom carried the effluvia, and afterwards the decayed blossoms, over a small breadth of this field to a considerable distance; and wherever they fell, the wheat was blasted" (22). With faith in that pattern, the grand epidemiological campaign began in America in 1918. Posters to "Free the 13 States From the Menace of the Red Tyrant!" plus Boy Scouts, garden clubs, and dirt farmers did the job. When Minnesota counties offered a bounty in the 1950s for wild barberry, they had no taker (15). The campaign to eradicate barberry was won.

A result close to his own work would have pleased Stakman. About 60 years later, races were less diverse east of the Rockies, where barberry was eradicated,

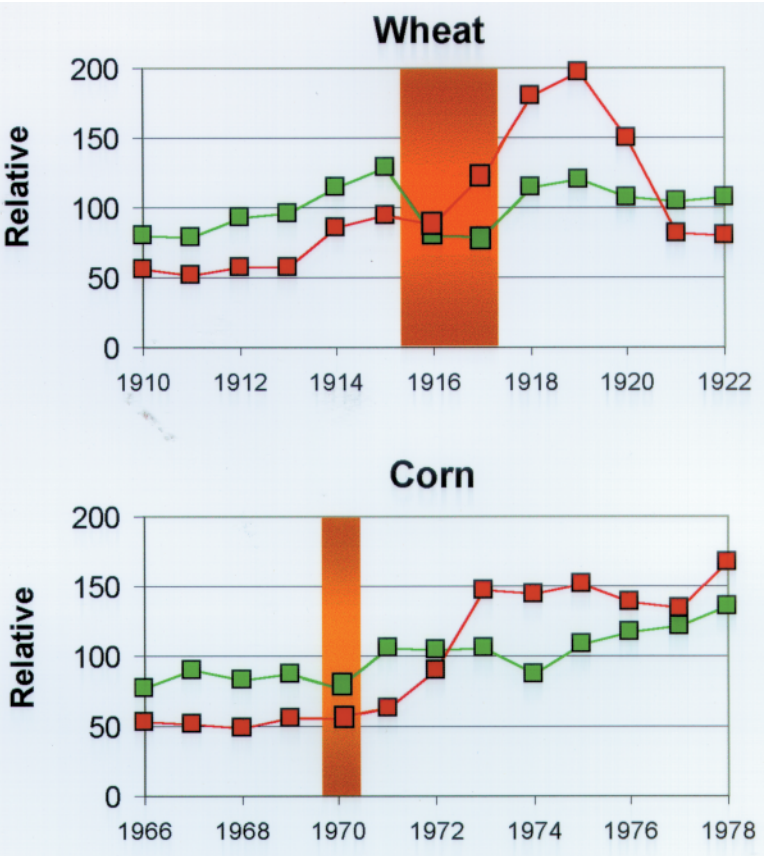

Figure 3 The impacts of two famous twentieth-century epidemics on the tons of US wheat and corn (*green squares*) and their dollar values (*red squares*). The upper shows the effect of the 1916–17 epidemic of rust on the tons and dollars of US wheat production during the Great War. The lower shows the effect of the blight epidemic on the tons and dollars of 1970 US corn production. The tons and dollars are expressed relative to 13-year averages.

than west of the Rockies, where barberry was not (67). This difference capping a grand epidemiological demonstration would have let Stakman sleep.

Diversities of Crop and Pathogen Evolve

Beyond the simple knowledge that genes differ, population genetics encompasses the dynamics of evolving pathogen and host genes. In 1970, a new pathogen in its first attack caused an epidemic so widespread that it affected the national average yield of the vast US corn crop (Figure 3, see color plate). The lack of diversity in corn underlying the epidemic brought to the fore studies of the interaction and evolution of crop and pathogen.

Theoretically, genes for resistance will be selected against if they impart no protection, and genes for virulence will be selected against if they are not required for pathogenicity (56). In real fields, different resistant hosts did select different virulence genes of powdery mildew differently (89).

Theory and experiments reinforced van der Plank's advocacy of horizontal resistance spread against all races. The hard knock of the corn epidemic added still more force to encourage *rediversification* (57). Self-conscious deployment of diversity to combat disease over wide regions had already been discussed for conserving resistance to oat crown rust (10).

On a smaller, simpler, and more manageable scale, simply mixing varieties promptly rediversifies a field. Theoretically, the diversity of cultivar mixtures (or multilines) should slow pathogen progress (49), especially highly variable mildew and rust pathogens. "The multiline theory ... is one of the truly new concepts this century" (9).

Mixtures of oat varieties show the theoretical slowing of disease progress—but with an interesting complication. Scattering varieties at random slowed progress more than concentrating them in blocks. An epidemiological model explained. When varieties are scattered, propagules suffer more dilution and hazard on the trip to another susceptible plant than in a homogeneous block of a susceptible variety (62). Theory and models compared to experiments have played a large role in studying mixtures. So, at the end of the century, experiments with mixtures as well as theoretical investigation of how mixtures change pathogen evolution are in order (58).

Diversity Overwhelms a Fungicide

Analogs of horizontal and vertical resistance crop up in fungicides. Old timers like Bordeaux mixture might be considered horizontal and so do not expose diversity in pathogens. New fungicides are analogs of vertical resistance that exposes diversity.

For years the systemic fungicide metalaxyl (Ridomil) effectively controlled two important mildews: tobacco blue mold and potato late blight. For example, between 1981 and 1995, metalaxyl practically kept tobacco blue mold out of Connecticut. A cloud already loomed in the 1980s, however, as reports of metalaxyl-resistant strains of *Phytophthora infestans* came from Ireland (21) and of *Peronospora tabacina* from Central America and Mexico (88). Nevertheless,

no epidemic of blue mold occurred in the United States until 1995 when strains resistant to metalaxyl attacked tobacco throughout southern areas. By season's end in 1996, a blue mold epidemic had raged northward all the way to Connecticut, where the fungus was highly resistant to metalaxyl. In 1997, metalaxyl-resistant strains dominated blue mold epidemics across eastern North America. The once-effective fungicide succumbed to the changing genetics of the shifty pathogens. By 2000 AD, epidemiologists knew how to mine the diversity of hosts for resistance, but they had attended schools of hard knocks taught by shifty pathogens overwhelming resistant varieties and even fungicides.

DISEASE LOSS

While the microbiologist concentrates on the pathogen from inoculation to dispersal, the epidemiologist and farmer include disease loss, too. They ask whether dollars for control will be repaid in harvested tons and dollars. Amplified in 1962 by Rachel Carson's *Silent Spring*, their question elevated *less chemical* to par with *less disease*. It evoked the integrated pest management and underlying disease monitoring and forecasting that filled the rest of the century.

Tons

As physical scientists, epidemiologists began with the physical tons lost to disease. In an unpromising start at the middle of the century, Large (54) found that fungicides that prolong growth of potato vines did not increase tons of tubers. Three quarters of the way through the century, epidemiologists had nevertheless measured enough percents of plants infected and subsequent yields to show progress. The percent infected at single critical times or at multiple points in time, or the area-under-the-disease-progress curves do correlate with the tons harvested. "The multiple point models, although more demanding in resources, provide the maximum flexibility and can cater for short or long epidemics where the onset, rate and level of infection may vary" (43).

While epidemiologists were correlating disease and tons lost, others were setting the stage for a generalization encompassing the effects on yield of foliar disease along with sunshine and leaf growth. With a remarkable similarity among species of healthy plants, the growth of leaf area and its absorption of sunlight determine the photosynthesis adding up to the yield of plants. Sunlight makes yield at the rate of 1–3 g yield per mega Joule sunlight absorbed. Earlier and more persistent leaves absorbing more of brighter sun during longer days make more tons.

If one simply subtracts the percentage of leaves infected from all those absorbing radiation, does this generalization simplify the explanation of disease loss? At least for a range of foliar diseases in three different crops over a span of varieties, years, and continents, it does the job (82).

Several benefits flow from this simplification. It aligns and permits comparisons of experiments in diverse seasons, climates, crops, and diseases. By placing disease loss assessment within the general realm of photosynthesis, micrometeorology,

and yield research, it permits use of their parameters, such as the proportionality between sunlight absorbed and tons yielded. It provides a standard for whether lesions emitting toxins or their location within the canopy complicate their simple decrease of healthy area. It provides a way of adding how much multiple pests cut the yield in tons.

Dollars

Although epidemiologists began with the physical tons lost to disease, the estimation of lost dollars did not remain simply multiplication of tons lost times price per ton. Such simplicity overlooks the common sense that scarcity caused by, say, disease raises the dollars per ton and moderates or even reverses farmers' loss. How much price counters the blow struck on farmers' dollars by tons lost depends on whether an inelastic demand for the crop keeps people consuming it despite higher prices (65). That generalization, of course, also needs qualification, which we shall add later.

The century illustrated tons and dollars lost with two notorious examples (Figure 3, see color plate). Before rust struck American wheat during the Great War, the conduct of war encouraged more tons and raised the dollar value of the American crop. When rust cut the 1916 tons by one third below the 1917 tons, an approximately 50% increase in price kept the dollar value of the crop about the same. During the next year, tons rose by little, but price again rose by nearly half, making the diminished crop even more valuable in dollars than the pre-rust crop.

The Southern corn leaf blight epidemic of 1970 cut tons and dollars relatively less. Also, it played out in different circumstances (23). During the years 1966–1978 encompassing the epidemic, world corn consumption was rising, but production was rising even faster. Just before the epidemic, world stocks were 22% higher than at a low point four years before. In this relative abundance, the world corn crop fell only 1% when the dramatic outbreak of the new blight cut the 1970 American crop by 11% below 1969. Since the stock of grain worldwide fell from only 15% to 13% of consumption, American farmers were lucky that a 15% rise in the price of corn made their smaller 1970 crop slightly more valuable than their pre-blight 1969 crop. They were also lucky that a prompt solution of epidemiological and technical problems by an effective infrastructure allowed them to produce a bumper crop in 1971, and that rising consumption and depleted stocks held up the price, making post-blight crops more than twice as valuable as before.

The sophistication that economics brings to epidemiology encompasses concluding that disease profits rather than costs farmers' dollars. Smith et al (72), however, finessed this sophistry by writing, "Total benefits to society cannot be increased by wasting effort ... by destroying part of products already produced, even though by such acts it may be possible to increase the income of a part of society by greatly reducing the income of the rest of society." The real loss to the world inflicted by, say, a potato disease is not the tons of potatoes of the untaken harvest or the dollars they would have been worth had the disease been absent, but the land,

the labor, and resources to grow these ungathered tons. Ordish (65) supported this conclusion by tabulating the annual 8 million ha of untaken harvest in the United States alone during the late 1930s, which disease rather than humanity took.

At the end of the century, epidemiologists could empirically estimate the tons lost to foliar disease by correlating it with disease at several times, and they could estimate it generally by integrating the sunlight absorbed by healthy leaves. They knew well that the rising price during scarcity caused by disease moderates farmers' economic losses. In an environmental era, however, they also knew that growing an untaken harvest by failing to control disease took land from Nature.

MANAGING

During the short run, farmers managing fields decide from week to week whether to take a control from the shelf and use it. In the long run, farmers and their supporters managing an industry place their bets on kinds of control and lines of research to defend a crop from diseases. They bet on expanding a healthy industry, or if disease threatens the crop at its core, shrinking or even abandoning the industry. With an abandoned crop goes the hard-earned skill of growing and selling it, plus the infrastructure of markets and the machinery and facilities to get it to the markets.

Short-Term Decisions

If disease threatens after farmers have planted a crop, they can take fungicides from the shelf to protect a valuable crop. Although regular spray seems safe insurance, it exacts a premium in dollars and sometimes in harm to the crop. Their dramatic response to weather made the downy mildews logical subjects for forecasting. By the quarter mark of the century, epidemiologists were devising forecasts to encourage more effort when mildew was imminent, but to save the premium of costly sprays and possible crop injury when disease was unlikely. Van Everdingen (81) devised simple rules that dew and clouds followed by rain plus warm night temperature would be followed by potato late blight within a fortnight. By the halfway mark of the century, Beaumont (7) revised the rules to fit Britain and simplified them to read relative humidity greater than 75% and minimum temperature over 10°C for two consecutive days would be followed by blight. Then Large (55) reduced Beaumont's rules to a spreadsheet spanning Britain that successfully anticipated early outbreaks. A negative forecast, telling farmers when a spray would be wasted, serves as well as a positive one (77, 86). Although typical disease forecasts only predicted the outcome of weather that had already occurred, synoptic weather charts were first brought into practical use in Ireland in 1952 and continued to be an integral part of prediction for weather *and* disease (8). At the three-quarter mark of the century when computers had arrived, Krause & Massie (52) computerized in Blitecast a system of blight periods that JR Wallin and RA Hyre had developed.

In the second half of the century, awareness added environmental side effects to the costs of chemical and crop injury that had long been considered before spraying. The focus of disease forecasting on spraying made it a crucial part of the integrated pest management (IPM) that environmental awareness called forth. IPM integrated disease forecasting with sanitation, scouting, and resistant varieties to control disease with less fungicides.

Communication, whether of observation coming from the field or warning going to farmers, lies at the heart of forecasting and makes the internet a boon to forecasting. A search of the web in 1999 found forecast research or practice in Germany, Britain, Canada, China, and ten American states. Mildews dominate the list of diseases.

Although forecasters concentrate on the weather, they have not forgotten that pathogens and hosts are essential. The name of the American organization that developed blight forecasting, the Plant Disease Survey, proclaimed the need for inoculum. Epidemiologists developed models of aerial transport of pathogens to calculate the probability that invading inoculum would arrive to ignite an epidemic (3, 20). To the quantity of invaders, forecasters must add a change in the pathogen's ability to surmount resistance or fungicides.

In a fitting climax to the century, Germans were supporting decisions about growing cereals, including disease control, with a single CD-ROM called PRO-PLANT (29).

Long-Term Bets

As the century began, the coffee growers of Ceylon exemplified placing a big long-term bet. Rust had attacked their crop for several years, and Ward had come and gone back to the home islands to write chapters on epidemiology. The growers made the extreme bet of abandoning the national crop of coffee and replacing it with plantations of tea (12). In an exemplary long-term appraisal, Miller (60) accurately predicted that the European climate would allow tobacco blue mold to inflict damage if it were introduced on that continent.

The corn blight of 1970 caused the placing of a long-term bet. The United States seed corn industry abandoned the convenience of making hybrid seed without the labor of detasseling because it deemed the accompanying hazard of genetic homogeneity too great.

The rediversification proposed in the wake of the corn epidemic qualifies as a long-term bet with nearly as great scope as abandoning hybrid seed made without detasseling. Arranging a nation's crops in small versus large fields qualifies as another large long-term bet. In 1960, van der Plank (79) theorized that large fields would be better because a few large fields could be farther apart than many small fields. His conclusion against small fields, however, depended on a one-dimensional model of dispersal, a small speck inevitable on the career of an original genius.

Reasoning at the limit of knowledge, van der Plank exemplified that wisely placing large bets can be hard. Every farmer who bet on corn versus soybeans, on

genetically engineered versus conventional varieties, or on planting a river bottom that sometimes floods knew that already. By diminishing the security from diverse people going in different directions, however, the very large scale of regional or national bets puts a larger premium on wisdom than one farmer choosing a crop. At the end of the twentieth century, surveys, instantaneous communication, and forecasts guided day-to-day decisions about spraying. Although long-term decisions were guided somewhat by experience, uncertainties still undermined faith in bets as large as placing a nation on a regime of horizontal versus vertical resistance, deploying its resistance genes, or scattering versus concentrating its crops.

WORK FOR THE TWENTY-FIRST CENTURY

As the nineteenth turned into the twentieth century, Englishman Ward (87) concluded one of his epidemiological chapters, "If we knew the damage done to all crops even in our own Empire, the results would probably astonish us." As the twentieth turns into the twenty-first, century Ward missed the end of Empire. He also missed the breeding for resistance and exposing races, which were already transforming epidemiology. He missed the aerobiological views that his student's student would soon see at the top of a ladder. Seeing how fallible foresight is, we stick to a conclusion so broad it cannot be wrong.

Whether in medical or plant epidemiology, the preeminent killers and disrupters are new invaders.

Although the evidence of potato late blight and grape phylloxera would have supported Ward in concluding the same in 1900, easier spread brought by globalization makes it easier for us in 2000. The conclusion that new invaders are what really matters suggests two lines of work: One for disease detectives to sleuth out new disease, and one for analysts of past disease to make firmer foundations to cope with new invaders.

New invaders, such as HIV, Ebola, and West Nile virus, challenge medical epidemiology too, and plant epidemiology can find a model in medicine's apotheosis of the disease detective. For example, the Secretary of Health and Human Services emphasized the new leader of the Center for Disease Control is a disease detective (70). Plant pathology's response to the corn blight pathogen in 1970 and to discerning metalaxyl resistance in Europe in 1981 requires no apologies. Nevertheless, bringing detection of new plant pathogens on a par with analysis of past epidemics would surely help cope with the inevitable new, dangerous, and disruptive invaders.

We mentioned forecasting disease to concentrate control when it is needed, computing the probability of airborne invaders to arrange crops across a nation, and deploying resistance and fungicides to forestall shifty pathogens. When we look for realizations of these grand schemes that so abundantly flow from analysis, however, we find disappointingly few.

Such grand schemes certainly have leverage to avoid or cope with the havoc of once-in-a-lifetime epidemics. Of course, the surprise and rarity of new invaders

joins cost and risk in discouraging realization of vast schemes. Nevertheless, the great impact of new invaders and high hopes of analysts for realizing their schemes encourage work on the second task. The task: To make the foundation of analysis so solid, the reconciliation of conflicting conclusions so complete, and the application to new invaders so clear that the world can confidently bet on them.

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