Healthy plants: necessary for a balanced 'One Health' concept

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Summary

All life forms depend ultimately upon sunlight to create the energy 'currency' required for the functions of living. Green plants can make that conversion directly but the rest of us would perish without access to foods derived, directly or indirectly, from plants. We also require their fibre which we use for clothing, building and other purposes. However, plants, just as humans and animals, are attacked by pathogens that cause a myriad of symptoms that can lead to reduced yields, lower quality products and diminished nutritional value. Plant pathogens share many features with their human and animal counterparts. Some pathogens – whether of humans, animals, or plants – have nimble genomes or the ability to pirate genes from other organisms via mobile elements. Some have developed the ability to cross kingdoms in their host ranges. Many others share virulence factors, such as the type III secretion system (T3SS) or mechanisms for sensing population density, that work equally well in all kingdoms. Certain pathogens of hosts in all kingdoms rely upon insect vectors and use similar mechanisms to ensure dispersal (and sometimes survival) in this way. Plant-pathogen interactions have more direct consequence for humans when the microbes are human pathogens such as *Escherichia coli* 0157:H7 and *Salmonella* spp., which can contaminate fresh produce or when they produce metabolites, such as mycotoxins, which are harmful when consumed. Finally, national biosecurity concerns and the need for prevention, preparedness and forensic capabilities cross all kingdom barriers. Thus, our communities that focus on one of these kingdoms have much to learn from one another and a complete and balanced 'One Health' initiative must be tripartite, embracing the essential components of healthy plants, healthy animals and healthy people.

Keywords

Animal, Disease, Health, Human, One Health, Pathology, Plant, Public health.

Salute delle piante: un requisito essenziale per un concetto "Una sola salute" equilibrato

Riassunto

Tutte le forme di vita dipendono, in ultima analisi, dalla luce del sole per creare la "corrente" fondamentale per la loro esistenza. Le piante verdi effettuano questa trasformazione direttamente, la sopravvivenza delle altre forme di vita, invece, dipende direttamente o indirettamente dalle piante stesse. Tuttavia, come uomini e animali, anche le piante sono attaccate da agenti patogeni in grado di ridurre la loro produzione, la qualità dei prodotti e il valore nutrizionale. Questi agenti patogeni hanno molte caratteristiche in comune con quelli dell'uomo e degli animali. Alcuni, siano essi diretti all'uomo, agli animali o alle piante, hanno genomi flessibili o sono in grado di sottrarre geni ad altri organismi attraverso elementi mobili. Altri hanno

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sviluppato la capacità di oltrepassare le barriere tra Regni per attecchire in organismi ospite. Molti altri condividono fattori di virulenza, come il sistema di secrezione di tipo 3 o i meccanismi di rilevamento della densità di popolazione, parimenti efficaci in tutti i Regni. Alcuni agenti patogeni presenti in tutti i Regni utilizzano insetti vettori e meccanismi analoghi per assicurarsi la diffusione (e talvolta la sopravvivenza). Le interazioni pianta-agente patogeno hanno conseguenze più dirette per l'uomo quando i microbi sono agenti patogeni dell'uomo come Escherichia coli *0157:H7 e* Salmonella *spp., che possono contaminare frutta e verdura o quando producono le micotossine. Le problematiche di biosicurezza a livello nazionale e la necessità di attuare programmi di prevenzione e intervento e le competenze di medicina legale interessano tutti i Regni. Pertanto, tutte le comunità che si concentrano, anche su uno solo di questi Regni, hanno molto da apprendere le une dalle altre. Un'iniziativa "Una sola salute" equilibrata e completa deve essere tripartita, ovvero comprendere gli elementi essenziali della salute delle piante, degli animali e dell'uomo.*

Parole chiave
Animale, Malattia, Patologia, Pianta, Salute, Salute pubblica, Umano, Una sola salute.

Introduction to plant health

The 'One Health' concept that has taken shape over the past two years, due in large part to the vision, thoughtfulness and energy of three of its 21st century leaders, namely: Thomas Monath, Laura Kahn and Bruce Kaplan, has focused on the critical interdependence between human and animal health and acknowledges the overlapping domains and impacts of environmental health upon these two disciplines. This concept of intertwined issues, purpose and goals makes very good sense, for many reasons that are explained in the early 'One Health' papers and American Veterinary Medical Association (AVMA) Task Force Report (3, 16, 24, 48). These include common issues such as zoonotic (cross-kingdom host) pathogens, niche adaptation, epidemiology, vector transmission, culture resources, food safety, biosecurity, pathogenicity mechanisms and strategies for research and synergistic collaboration.

Although the importance of plant pathology/plant health in the 'One Health' movement has been recognised recently and the discipline welcomed by the 'One Health' community, the specific role of plant health in the movement has not been clearly defined. Then, a year or so ago, a plant pathologist (Jacqueline Fletcher) was invited to join the 'One Health' initiative and the need to add plant health to the initiative was clearly logical. Our fates are linked. Plants are both directly and indirectly essential for human and animal health. The food chain consists of four essential parts, namely:

- the energy of the sun
- the producers (plants, which provide glucose and oxygen)
- the consumers (herbivores, which eat plants; carnivores, which eat other animals; parasites, which live off of other organisms; and scavengers, which eat animal carcasses)
- the decomposers (bacteria and fungi, which convert waste into fundamental breakdown products, such as carbon and nitrogen).

The cycle repeats itself efficiently and sunlight energy moves through the food chain, some of it eventually being converted into heat that radiates back into space. Without plants, the transformers of solar energy, humans and animals would lack food and oxygen and, without the sun, the earth would be cold and all life would cease. Plants, although generally relegated by humans to the bottom of the priority list, are absolutely essential to our survival. Apart from providing the essentials mentioned above, plants also are a major source of fibre for clothing and structural materials for housing throughout the world.

In addition to a nutritional link, issues of concern to human and animal health specialists – cross-kingdom pathogens, vector transmission of pathogens, food safety, understanding pathogen virulence, bio-security, and research needs – are just as relevant for the plant scientist. There are many examples in which research in human and veterinary pathology has facilitated and supported similar work in plant health, and – without doubt – examples from the plant world have equally informed the study of pathogens of people and animals.

In this paper, a plant pathologist is joined by a veterinarian and a food safety specialist to highlight some of the most important ways in which our fields are inexorably blended and to define the critical intersections among them. Our goals are to increase awareness of the critical role of plants, not only in human and animal health, but also in their own right as the framework of our environment. The AVMA One Health Task Force has defined 'One Health' as 'the collaborative efforts of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and our environment'. We believe that a truly balanced and effective 'One Health' concept will include language that specifically recognises the role of plant health and propose a slightly modified definition for the consideration of our readers, as follows: 'One Health is the collaborative efforts of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, **plants** and our environment'.

The discipline of plant pathology/plant health: history and perspectives

Although plants, as the initial energy currency exchangers, are essential for all human and animal life, their health is generally regarded as a lower priority than that of other life forms on earth. Yet, critical plant resources, including crops, rangelands and forests, are susceptible to a wide range of fungal, bacterial, viral and nematode pathogens. Throughout history, the impacts of plant diseases have been manifested in damage to human health and well-being (1, 25, 38). Early civilizations were aware of plant diseases and a number of passages in the Bible refer to blights, blasts and mildews. Aristotle and Theophrastus wrote about plant diseases in the 3rd century BC, and grain production in Europe during the Middle Ages was plagued by the ergot fungus. A plant disease, wheat mildew, was even mentioned by Shakespeare in one of his plays. At that time, plant diseases were believed to generate spontaneously from 'degeneration' or 'night air'. In the 700s, the Romans battled against wheat stem rust, caused by the fungus *Puccinia* sp., by holding pagan rituals to appease the god Rubigo, who brought the red, powdery fungal spores to their crops. In the early 1900s, Irish peasant farmers, barely subsisting on their own small shares of the potato crops they cultivated for their landlords, were devastated by *Phytophthora infestans*, an insidious fungus-like oomycete that destroyed their crops and led to the starvation of a million Irish citizens, as well as the emigration of another 1.5 million – many to the United States – in search of a better life. World War I inflicted many casualties in Europe, but few realise that plant diseases significantly influenced the course of the war; the cold, damp conditions of 1916-1917, in both Europe and the United States, favoured rapid propagation and dissemination of wheat pathogens and the meagre harvest on both continents was insufficient to sustain planned troop deployments. At about the same time, another fungus was devastating the coffee crop in Ceylon, a colony of Great Britain, changing forever British preferences for hot beverages from coffee to tea.

In the late 1800s, Anton de Bary, later dubbed the father of plant pathology, published a book identifying fungi, for the first time, as the cause of a number of plant diseases and introducing the germ theory of disease. During the rest of the 19th century, other scientists in many countries further clarified the role of microbes – including bacteria, viruses and nematodes, in addition to fungi – in plant maladies (1, 38). After World War II, the corn belt states of the United States suffered a severe epidemic of corn leaf spot, a malady caused by the fungus *Peronospora maidis*, the impact of which was exacerbated by the previous incorporation of resistance genes into a particular maize variety which was planted in a virtual monoculture. The economic impact of this disease was severe throughout the rural Midwest. Fungicides were developed in the

1940s and nematicides in the 1950s. In the 1960s, Japanese scientist Y. Doi discovered mycoplasmas, wall-less bacteria and, soon after, in 1971, the United States Department of Agriculture (USDA) plant pathologist T.O. Diener, discovered viroids, pathogens even smaller than viruses.

During these formative years of plant pathology, huge strides were also being made also in human and animal medicine and these disciplines were influenced by some of the plant pathology discoveries (14). For example, although fungal diseases of humans can range from common, minor ailments (athlete's foot) to potentially fatal systemic infections, these fungal pathogens of humans are less well-studied than human pathogenic bacteria and viruses. On the plant side, however, fungi cause over half of all significant plant diseases and plant pathologists are at the forefront in understanding fungal metabolism, biology and pathogenicity. Other discoveries and important scientific advances happened first in the plant world; for example, 1935 was a landmark year for biology when plant pathologist W.M. Stanley received the Nobel Prize for the first description of a virus as a coat of helically arranged proteins surrounding a nucleic acid core. Particles of his tobacco mosaic virus were the first viruses ever visualised by electron microscopy just a few years later. In the bacterial realm, plant pathologists were the first to recognise two new taxa of micro-organisms, the spiroplasmas, which are helical mollicutes, and phytoplasmas, their non-helical relatives. With the exception of *Mycoplasma penetrans*, human and animal mycoplasmas were considered to be extracellular pathogens and it was in the plant realm where penetration into the cytoplasm of host cells (in both the plant host and the insect vector) was first recognised to be the norm (17, 18). Plant pathologists also led the way to understanding certain virulence mechanisms; Brian Staskawicz and Noel Keen, working with the bacterial plant pathogen *Pseudomonas syringae*, were the first to discover and describe the (T3SS) that is now recognised as a common virulence factor in pathogens of humans and animals, as well as in those of plants. Finally, the first reports of small RNA-based gene silencing and its impact on the action of pathogens within their hosts, came from British plant pathologist James Carrington (14). These important contributions from the discipline of plant pathology have helped to shape understanding of human and animal pathogens as well.

Links between plant, animal and human health

Food

Plants are intimately linked to human and animal health through the realm of food: its sources, distribution, and consumption. The essential nutritional contribution of fruits, vegetables, grains and other plant products at the bottom of the food triangle has already been mentioned. **Food safety** (the absence of harmful elements in our food) and **food security** (the assurance of consistent availability of safe and nutritious food) are concerns of central relevance to the 'One Health' concept. With respect to food security, the world's population faces two extremes: on the one hand, an ever-increasing number of the world's population lacks sufficient food to sustain life and health; on the other, alarming obesity rates in both adults and children have led to a condition described as the first epidemic of the 21st century. Both of these crises have consequences that will last through much of this century. Plants, plant engineering and plant disease reduction are critically important to resolving these global problems.

Food safety issues, though of high visibility in the United States in recent years due to serious outbreaks of foodborne illness, are minor in this country compared to the situation elsewhere. Worldwide, 1.5 million people, mostly children, die each year of shigellosis and other diarrhoeal diseases caused by contaminated water and food. For those with a high standard of living, food is part of a sphere of life composed of things we cherish most; our health, family and relationships, spiritual beliefs, and culture. Food provides an interconnectivity of life: it is health giving and health sustaining; it elicits nostalgia of times past; its enjoyment is a centrepiece for our relationships and its rich diversity often a focal point of our cultural traditions. Although we often take our food for granted, when viewed on both a nutritional and a personal basis, food safety and security rise to a position of prime importance.

Statistics point to cause for concern. An estimated 76 million people experiencing foodborne illness annually in the United States (10) suggests that one in four Americans falls ill because of contaminated food each year. While most of these cases are not reported, 325 000 hospitalisations occur annually. The toll is high: 5 000 of these patients die and associated societal costs run to tens of billions dollars per annum. Not counted in these losses is the illness, or aggravation of illness, due to stress from the fear of unsafe food: parents buying food for an infant or for ailing parents; immunocompromised individuals who may be more susceptible to food contaminants; or the farmer or marketer for whom such losses might be the tipping point for a lost livelihood. Simply put, the fear of unsafe food causes anxiety that surely has its own health consequences.

A fascinating feature of the cases above is the significant and rising fraction caused by consumption of contaminated fresh produce, a recent phenomenon in the United States. *Escherichia coli* O157:H7, which lives asymptomatically in healthy cattle (29), was discovered as a human enteric pathogen in 1983 (34). Strain O157:H7 became known, unfairly to the beef industry, as the 'hamburger pathogen' in the 1980s-1990s because of its association with meat from fast-food restaurants. During the last decade, however, fruits and vegetables have been responsible for more foodborne illnesses than any other food group. Since first reported in 1991, leafy green produce has accounted for over 20% of foodborne outbreaks of *E. coli* O157:H7 (33). Similarly, nearly half of known outbreaks caused by the multiple serovars of *Salmonella enterica* have been linked to fresh produce, particularly tomatoes and melons. Outbreaks of *Shigella* and *Campylobacter* pathogens associated with leafy greens also have been observed (40). The phenomenon is a general one, then, raising the question whether enteric pathogens merely persist on plants, in the absence of animal hosts, or whether they have a specialised lifestyle for survival and growth on or within plants (see the excellent review by Brandl) (7).

The evolution of the ancient bacterial family *Enterobacteriaceae* to pathogenicity suggests that these bacteria might retain a capacity to survive and thrive in a wide range of environments, including plants. Comparative genomics of extant animal and plant pathogens limits this conclusion, however. The genome sequence of one member of the family, *Erwinia*, shows that this plant pathogen contains horizontally transferred genes supporting colonisation of plants, while the evolutionary backbone structure of its chromosome is similar to those of other enterobacteria, including *E. coli* and *Salmonella* (42). *Erwinia* spp., at some point, acquired genes for interaction with plants. Plant surfaces might provide a favourable environment where gene exchange occurs more readily than in other environments. These and other factors, such as internalisation, endophytic growth, nutrient release upon wounding, biofilm formation and increased fitness of enteric pathogens, are subjects for interdisciplinary research to understand – and help control – this recent phenomenon.

Foodborne outbreak control

Food safety concerns reach our attention when large multi-state outbreaks disrupt normal routines. In 2008, tomatoes were removed from the United States summer market due to a risk of contamination with *Salmonella* Saintpaul, a pathogen causing gastrointestinal illness. Over the course of three months, 1 438 cases and at least 282 hospitalisations were reported in the United States and Canada (11). The outbreak eventually became the most prolonged and complex foodborne outbreak in the modern era, as cases of illness continued to be reported even after removal of suspect tomatoes from markets. Only after re-examination of epidemiological associations and exhaustive searches for the pathogen was it determined that one likely contamination source was jalapeño peppers imported from Mexico (11). Tomatoes might have been involved as well, however; both foodstuffs were handled in a small distribution plant and both are used in common cuisines. The source of initial contamination was probably irrigation water, a resource in which ecology and environment combine to have an impact on human health. The consequences of this incident were dire for the United States tomato industry and for individual marketers; losses to the industry of US$100 million over the three-month period have been estimated.

Another recent large-scale outbreak that gained notoriety involved fresh produce, that is, the 2006 outbreak of *E. coli* O157:H7 in fresh spinach. The contamination was traced to a surprising scenario of wild pigs serving as vectors of bacterial contaminants in the run-off from cattle farms in California's Salinas Valley (23). Foodborne disease outbreaks are usually less consequential than these; most are rapidly traced to their source and, indeed, most instances of contamination are discovered by a diligent processor or distributor before human harm occurs. The examples mentioned above, however, serve to undergird the need for multidisciplinary approaches to understand and solve public health problems. In these cases, as stated in the *One Health Task Force Report* (2), 'Only by integrating our knowledge of the environment and ecology could this investigation be completely understood. More importantly, only through this knowledge can appropriate intervention and prevention strategies be properly implemented'.

Appropriate food safety responses

An effective food safety response programme must involve government, industry, markets, media and the consumer. Considerations that might guide our thinking are provided below; some are self-evident, but they warrant stating given recurrent concerns for safeguarding our food supply.

- Food safety is a public health issue. It is addressed by thousands of dedicated public health professionals who have the tools, expertise and experience to operate an effective system. While there is debate about roles for each sector of society in providing a safe food supply, the government has the responsibility to ensure safe and healthy food.
- Almost all food contamination is accidental, although the 2001 anthrax episode brought new awareness of the dangers of public exposure to pathogens. Except for this and a few biocrimes involving pathogenic bacteria that occur each year (9), the vast majority of outbreaks are unintended and transient; most of those, in turn, involve few people or are sporadic cases. The pathogen is the culprit; farmers, producers, processors and retailers strive to furnish safe food to the public.
- The first responsibility of government in response to a disease outbreak is to protect public health from further risk by prompt identification of the contaminant, location of its source and containment of the outbreak. Valid, rapid, and high-throughput methods must be used for sample screening. Following compliance requirements, the pathogen might be isolated from the implicated sample(s), but public exposure to it would have been stopped. Collaboration among the food safety, medical, engineering and biotechnology communities will facilitate the development and application of appropriate high-throughput screening technologies.
- Today's public health emphasis on food safety should be in the prevention of contamination. This is being done effectively through employing hazard analysis and critical control points (HACCP) to identify points in the production and processing chain that are most susceptible to contamination (43, 44). Promoting such smart risk management strategies will best protect public health.
- Other food safety responsibilities fall to the public. This is not to suggest a *caveat emptor* approach for the consumer but rather a call for using common sense. Many remember or still experience fresh food obtained from the backyard garden and carefully washed for

the dinner table; such preparations are no less important today. Recommendations for consumers include:

- wash fruits and vegetables before consuming them
- acknowledge that packaging alone may not guarantee safety
- accept new technologies, such as irradiation of food, which contribute to ensuring its safety.

Mycotoxins

Many fungi, including a number of plant pathogenic species, produce and export metabolic by-products called mycotoxins (fungal poisons) (6). These low molecular weight molecules of diverse molecular structure (5) are harmful to the host plant in which they may lead to aggravated disease symptoms. Mycotoxins also have an impact on humans and animals who consume contaminated plants, causing confusion, increasing susceptibility to human pathogens and other toxins and even death. Mycotoxicoses occur more frequently in underdeveloped nations where food storage conditions may be suboptimal and there is greater likelihood of consumption of contaminated foods or physical contact with fungal mycelia and spores on contaminated materials. Although mycotoxin effects are generally less frequent in developed nations such as the United States, those whose consumption of corn-based foods is relatively high, such as Hispanic populations, or who live in less affluent urban communities are more often exposed to mould-produced mycotoxins (4).

Little-studied prior to the early 1960s, mycotoxins gained visibility when peanut meal contaminated with aflatoxins from the fungus *Aspergillus flavus* were blamed for a mysterious disease called 'turkey X' in England, causing the deaths of an estimated 100 000 birds (6, 19). Other toxin-producing phytopathogenic fungi include *Cochliobolus*, *Alternaria* and *Fusarium* spp., all of which have well-established roles in plant disease development (15, 47). It is likely that certain fungi benefit from the production of mycotoxins by preventing food competition from other fungi or animals. Of the approximately 300 to 400 compounds now recognised as mycotoxins, about a dozen are viewed as threats to human and animal health (13). These include some previously recognised fungal toxins, such as the alkaloids produced by ergot fungi (6). Aflatoxin, produced by *Aspergillus*, is a polyketide-derived compound with hepatotoxic, mutagenic and carcinogenic properties, while the *Fusarium*-produced metabolite, zearalenone, mimics oestrogen in its activity (6).

Effective management of mycotoxins includes the implementation of 'best practices' at several points in the food production continuum, as follows: post-harvest drying of crops to minimise mould growth and good sanitation in pre- and post-harvest storage facilities (6, 26). Recent efforts have focused on development of plant resistance to mycotoxin-producing fungi, genetic enhancement of antifungal plant genes, deployment of biocontrol agents and blocking genes that trigger mycotoxin production (8). However, since such approaches are not, at present, acceptably effective it remains important to screen produce and value-added products for mycotoxin contamination (6).

Common elements of basic biology and pathogenicity of plant/animal/human pathogens

Fungi, bacteria, viruses, viroids, prions, protozoans and other microbes colonise and cause abnormal conditions in humans, animals and plants. Although plant pathogens must somehow circumvent or breach the plant cell wall, a significant physical barrier not encountered by human and animal pathogens; many of the mechanisms of host adaptation and colonisation and the determinants of pathogenicity and virulence share common elements across host kingdoms (Table I) (22, 32, 45, 46). Pathogens disrupt host cell or tissue function, compete with host cells for nutrition, produce virulence factors, such as toxins, enzymes or hormones, or trigger expression or repression of host genes. A few pathogens,

Table I
A few examples of cross-kingdom microbes
For a more extensive list see Vidaver & Tolin (46)

Pathogen	Human host	Plant host	Insect (vector) host
Bacterial pathogens			
Agrobacterium tumefaciens	Bacteremia	Tumours/galls on rosaceous plants	
Burkholderia cepacia	Cystic fibrosis, infections	Pink rot of onions	
Dickeya didantii (*Erwinia chrysanthemi*)	Experimentally invades human cells	Soft rots of chrysanthemum, potato, etc.	Pea aphid
Enterococcus faecium	Urinary tract infections, bacteremia, bacterial endocarditis, diverticulitis and meningitis	*Arabidopsis* (laboratory only)	
Pantoea agglomerans (*Enterobacteria agglomerans*)	Soft tissue, joint infections, bacteremia	Black spot necrosis of beach peas	
Pseudomonas aeruginosa	Cystic fibrosis, infections	Diseases of onions and wisteria	
Serratia marcescens	Opportunistic; septicaemia, infections	Wilt, death of cucurbits	Squash bugs
Spiroplasma kunkelii	NA	Stunting, reduced yield in maize	Leafhoppers
Staphylococcus aureus	Endocarditis, pneumonia, boils	*Arabidopsis* root infections, death (laboratory only)	
Fungal pathogens			
Alternaria spp.	Infections of respiratory tract, skin and nails	Wood rots	
Penicillium spp.	Lung infections	Post-harvest produce diseases	
Verticillium spp.	Eye infections	Vascular wilts, many plant hosts	

NA not applicable

such as *Agrobacterium tumefaciens*, the bacterium that causes crown gall of many plant hosts, genetically engineer their host cells, forcing them to abandon normal activities to more effectively support pathogen growth. Research on this unique pathogen, funded by the National Institutes of Health, gave medical researchers insights into mechanisms by which cells ignore signals of contact inhibition and proliferate into tumorous growths. *A. tumefaciens* will even invade and disrupt human cells when introduced to their environment in the laboratory (41). A small subset of virulence factors shared by pathogens of all three kingdoms (plants, animals and people) appear below.

Signalling systems, quorum sensing and biofilm formation

All cells, whether unicellular organisms or part of a multi-celled organism, recognise and respond to signals and conditions in their environment. The use of externally exposed membrane sensor molecules that detect extracellular conditions or signal and the translation of those perceptions via complex cascades of reactions involving molecular rearrangement, phosphorylation, electron transport and other events, are common among pathogens, regardless of the nature of their hosts. Many bacteria couple their signalling mechanisms with the sensing of a minimum population density (quorum sensing) and respond to the achievement of a quorum by triggering the expression of otherwise repressed genes encoding various products, including virulence factors. Other density-dependent gene expression, in a number of pathogenic bacteria, results in the deposition of a protective, structured extracellular milieu, or biofilm, composed of polysaccharides and other materials surrounding a bacterial community (37). Bacteria of different species, the same species or even the same genotype, residing in different parts of the biofilm, may perform different functions, express different genes, and ultimately play different roles in host interactions. The complexity of the signalling systems used, vary with pathogen genome size and with the type of host-pathogen interaction (39).

Gene regulation

Regardless of their environment, microbes conserve energy and enhance their ability to utilise the resources in their surroundings by turning gene expression on and off in an asynchronous manner. In the case of pathogens, genes involved in host recognition and adherence may be expressed early in a host-pathogen interaction, while genes encoding various virulence factors may be down-regulated until a population quorum is reached, at which time they may have escaped the activation of a host resistance response and also reached a population level suitable for translocation and colonisation of other host tissues. Such considerations occur whether the host is a human, animal or plant. A more recently discovered regulatory mechanism of bacterial pathogens is the production of small, non-coding RNAs (sRNAs) (27). These molecules, which often act as post-transcriptional regulators, attaching specifically to mRNAs and altering their stability and function, have been implicated in the expression of pili, sensory systems and other pathogenesis-related functions.

Secretion systems

Many human, animal and plant pathogens incite disease in their hosts by exporting toxins, enzymes, growth regulators, nutrients, DNA, adhesins and other molecules, synthesised within the pathogen cytoplasm or organelles, directly into host cells or tissues. Although the specific molecules and their targets vary with each system, many of these microbes use very similar molecular secretion systems, the most prevalent of these being the T3SS. While this strategy was first described in the human pathogen *Yersinia* spp. (35), it has since been identified in many other zoonotic and plant pathogenic organisms. In the case of many plant pathogenic bacteria that reside in the plant host's intercellular spaces, the T3SS may enhance nutrient leakage from adjacent plant cells or assist in resistance to host plant defence responses (31). Interestingly, T3SS associated genes in plant pathogenic bacteria were initially called 'avirulence genes' because their presence was associated with host resistance; later research showed that the products of the avirulence genes were specifically recognised by products of plant disease resistance genes, the recognition leading to activation of host resistance genes (31). T3SS genes bear the hallmarks of horizontal transfer and are believed to be readily exchanged among bacteria of different taxa, thereby accounting for T3SS similarities among bacterial pathogens of multiple kingdoms.

Another secretion system shared by human, animal and plant pathogens, the type IV secretion system (T4SS) is functionally tied to a number of pathogen activities, including conjugation, host colonisation, virulence, and vector transmission, in addition to the secretion of substances affecting pathogenicity and virulence. Some of the T4SS proteins bear remarkable similarity to those of eukaryotes and, further, many proteins secreted by this system also have eukaryotic protein-like domains (36).

Apoptosis

The ability of organisms to trigger the death of certain host cells is a factor in diseases of all kingdoms. Zoonotic pathogens *Bartonella* spp., *Brucella* spp. and *Helicobacter pylori* all use apoptosis as a factor regulating (positively or negatively) the immune response during an infection (20). In many cases, plants invaded by viruses, bacteria or fungi may display a visible, rapid, localised necrosis at the site of pathogen introduction. Rather than being considered a symptom of acute disease, this rapid cell death, known as hypersensitivity, effectively walls off the pathogen, preventing its further movement within the plant and limiting its uptake of plant-produced nutrients.

Receptors

Generally located on the exterior of the cell, receptor molecules are most often surface proteins that may undergo transformational changes upon selective binding of molecules in the extracellular environment. In most plant infections, the recognition of pathogen surface molecules by host factors leads to the activation of host resistance response pathways. Conversely, lack of recognition generally leads to disease development. The presence or absence of a polysaccharide capsule or slime layer outside the bacterial cell wall may influence recognition, such that encapsulated strains may be pathogenic while their uncoated relatives are not.

Attachment/adherence mechanisms

Bacterial surface appendages, such as fimbriae and/or pili, are often virulence-related, regardless of the type of host. Implicated in attachment to the host, conjugation and delivery of DNA and other molecules into a recipient cell, these structures are common to bacterial pathogens in all host kingdoms.

Can plant pathogens influence human and animal health more directly? The answer is clearly 'yes'

Cross-kingdom pathogens

It is well recognised that some pathogens can infect hosts in more than one kingdom (Table I). Many pathogens that are transmitted by other organisms, often insects but sometimes nematodes, protozoa, or members of other taxa, are two-kingdom colonisers. Those transmitted mechanically are generally just passive passengers, but pathogens transmitted circulatively or propagatively actively penetrate, colonise, multiply, cross membrane and even cellular barriers in their vectors and, in some cases, even cause disease in their insect vector. One remarkable example is the genus *Spiroplasma*, comprised of helical mollicutes related to mycoplasmas. Dozens of *Spiroplasma* species have been identified, but most are residents – sometimes, but not always, pathogens – of insects. Only three, *S. citri*, *S. kunkelii* and *S. phoenicium*, are known plant pathogens and even these three are transmitted by insects and likely arose as insect pathogens that were able to adapt to a new environment in the plant host phloem. Other well-known cross-kingdom microbes that are nosocomial pathogens of humans include *Burkholderia cepacia* which causes pink rot of onions and *Pseudomonas aeruginosa*, the causal agent of bacterial leafspot of tobacco, both of which are also implicated in human cystic fibrosis. Perhaps we also should consider human pathogens, such as *E. coli* 0157:H7 and *Salmonella* spp., in this category too, as we discover more about their potential to interact with plants in the field.

Approximately 75% of infectious human pathogens of emerging concern for their potential to be used as weapons are shared between humans and animals; these are called 'zoonotic agents'. Some, such as the equine encephalomyelitis viruses (alphavirus family), have complex life cycles involving mosquitoes, birds, rodents, equids and humans. Plants figure prominently in providing the habitat for successful breeding of mosquito vectors and providing a source of carbohydrate meals for those vectors required for survival and reproduction. Plants can either contribute (a bumper crop of pinion seeds) to the growth of rodent populations needed to spread a human pathogen, as in the case of the Sin Nombre virus outbreak in the 'Four-Corners region' of the United States in the 1990s, or, rarely, plants can contribute directly to human disease through dermal or oral intoxications.

Plant pathogen products in human medicine

Recently, plant pathogen-host research has brought new and exciting insights that may lead to novel treatments for human cancers. The plant pathogenic bacterium *P. syringae* pathovar syringae, the causal agent of a leafspotting disease of the common bean, was shown to secrete a previously unknown virulence factor, syringolin (SylA), *in planta* (21). This compound inhibits all catalytic activity of eukaryotic proteasomes, a previously unreported virulence mechanism.

Proteasome inhibitors have shown promise as anti-tumour agents, and this new class of compounds, designated syrbactins, may be useful in human drug therapy.

Vector transmission of pathogens

Relationships between pathogens and vectors

Pathogens of humans, animals and plants are disseminated by a myriad of mechanisms, but among the most complex systems are those that involve one or more vectors, organisms that transmit pathogens from one host to another. Most vectors are insects, such as the mosquitoes that transmit the *Plasmodium* species causing malaria, the 'kissing bug' vector of the flagellated protozoan that causes Chagas disease, the glassy-winged sharp-shooter that transmits *Xylella fastidiosa*, the causal agent of Pierce's disease of grapevines, or the whitefly that carries plant-infecting Geminiviruses.

Modes of transmission

Mechanically transmitted pathogens are generally acquired by direct contact with a part of the insect's body and are similarly knocked, rubbed or wiped off in or on a new potential host organism without any active participation on the part of host, insect or pathogen. More intimate associations occur when pathogens are ingested by the vector insect and colonise within its body. Foregut-borne pathogens form communities on the inner surfaces of the anterior regions of the alimentary canal, whereas circulatively transmitted pathogens traverse the insect gut wall, entering the body cavity or hemocoel, in which they circulate. Such pathogens can later be transmitted to a new host during insect feeding. Propagatively transmitted pathogens are similar to circulative ones, with the added feature of multiplication within the hemolymph; the pathogen may reach very high titres in such insects, resulting in a high probability of inoculation when the insect feeds on a new host. Pathogens that colonise and multiply in their vectors are interesting because of their adaptation to life in two very different types of hosts. Fascinating work in both human medicine and plant pathology has just begun to provide insights into the regulatory mechanisms that turn some genes on and others off in the primary host, and activate or repress different gene sets in the vector species.

Specificity

Specificity between the insect and the pathogen, or between the insect and the host, is common and may result from factors of host range, pathogen evasion of insect digestive enzymes and/or the insect's immune system, recognition between pathogen and insect vector tissues, ability of the pathogen to traverse insect barriers and/or to utilise insect hemolymph as a nutrient source. In addition, residency of the pathogen within an insect environment, whether it is the interior mouthparts, the gut lumen, the hemolymph, the salivary glands, or the ovaries, may affect pathogen virulence. Such factors are relevant to disease incidence, epidemiology, spread and management regardless of the kingdom affiliation of the host species. Research findings from such studies often are valuable to all health communities.

Management

Finally, management of insect-borne pathogens often involves managing the vectors and similar mechanisms for reducing vector populations may be utilised in human, livestock and plant environments. Other approaches that can be valuable in the management of plant diseases and, to a more limited degree, animal diseases, include the use of breeding or genetic engineering to create plant cultivars or animal lines resistant to the pathogens or to their vectors.

Biosecurity

Vulnerabilities

All enterprises associated with the food chain are vulnerable to disruption. Humans are free to travel, work, play or reside as they desire and/or to the extent they can afford. Food animals, housed and managed in large concentrated facilities, are transported widely on public roads. Plants grown for food or fibre, usually as monocultures, are broadly dispersed in rural and remote areas where they receive very little oversight. All species may be exposed to pathogens or pests through natural, accidental or intentional means, but levels of vulnerability vary depending upon multiple factors, such as product value, frequency and thoroughness of monitoring, and susceptibility to pathogens and pests. Behaviours and 'intent' of humans can either increase or decrease the risk of disease in all three kingdoms. Good animal and plant husbandry can reduce the disease burden on individual animals and plants as well as on populations.

Prioritising life forms

In our society, human life is valued much more highly than animal life – as it should be – and animals are typically seen as more valuable than plants. The health of individual humans is usually more closely monitored – and preventive medicine practised more seriously – than that of either animals or plants, but the hierarchy of care and concern is neither universal nor homogenous. Some pets and working animals and some valuable plants are better protected and cared for than are some humans. However, broadly across the kingdoms, a hierarchy exists within the food chain.

Even natural variables contributing to biosecurity across the spectrum of life, whether to natural, accidental or intentional pathogen infection or invasion, are nonlinear. Human disease might occur in a congested city after an intentional release of a stable pathogen or through the natural introduction of a communicable one. Only a few pathogens, such as bacterial spores and infectious, contagious viruses, could be ideal weapons against humans. Yet, because of the responsive nature of our human health care system, an outbreak is often noted shortly after the first members of the population become ill. The result of a human outbreak is real, emotional and costly. Animals in herds or flocks, like humans in congested cities, are most vulnerable to highly infectious or contagious viruses. Large outbreaks, such as the foot and mouth disease (FMD) epidemic in the United Kingdom in 2001, typically cause a broad and deep economic impact with many indirect costs. For the individual farmer or rancher, such an outbreak can be emotionally traumatic because of loss of both livelihood and valued animal life, especially when breeding animals held for years for milk or wool are lost. Although plants also can be damaged by bacteria or viruses, fungal infections and insect pest invasions are more common and cause significant economic losses. However, because crops are grown over huge, unmonitored acreages, pathogen introductions, although sometimes predictable years in advance (unlike outbreaks in humans or animals), may go unnoticed for many months and then, after diagnosis, can be extremely difficult to manage. Given that our relationships with plants are almost purely economic, a huge outbreak that might bankrupt a small or medium-sized Midwestern farming community will hardly be newsworthy on the coasts. Only when the decline in plant productivity reaches a level that affects the supply of animal feedstock, or raw materials for clothing or shelter, does the human population take notice. So, while we are inextricably linked to our animal and plant kingdom travelling partners, the agents of concern and the outcomes of disease on the populations, differ.

Environmental effects on disease threat

The impact on and spread of disease through a population, whether human, animal or plant, can vary with weather, proximity to other susceptible individuals of one's own kingdom or members of another, husbandry, preventive medicine or population resistance. Seasonal winds or storms, such as hurricanes, can transport pathogens and insects which can infect new plant populations hundreds of miles from their source. Climate change, or simply changes in rainfall, can alter the dominance of plant species as well as of mosquitoes or other vector insects and facilitate spread of disease to new populations of humans, animals or plants. Husbandry practices, such as indoor housing of poultry flocks or swine herds, or the protection of valued plants (seed or grafting 'mother plants' for example) within screen houses, can reduce the likelihood of pathogen and pest introduction. The presence of resistance in even a subset of a population, such as the result of vaccination of humans or animals, or genetically engineered resistance in a plant population, can reduce the likelihood that introduction of a disease-causing organism will cause major damage.

Epidemiology

Epidemiological patterns of a disease outbreak may be quite different if it is naturally introduced than if it is intentional. Natural or accidental introductions are typically focal and involve only one pathogenic agent, while intentional introductions could be multifocal or involve more than one pathogen or pest. The geographic location of a natural or accidental introduction is generally logical, based on transportation routes, weather, or vector movements, while that of an intentional outbreak might not be so.

Policy issues

Legal prohibitions against intentional introduction of pathogens into human, animal or plant populations are clearly stated in the Biological Weapons Convention of 1972. Furthermore, United Nations Resolution 1540 calls for individual states to 'establish domestic controls to prevent proliferation' of biological and other weapons of mass destruction. Before signing and ratifying the Biological Weapons Convention in 1972 and 1975, respectively, the United States developed not only anti-personnel and anti-animal weapons but also anti-plant weapons, ostensibly for use against Soviet wheat crops and Chinese rice paddies. Rice blast, rye stem rust and wheat stem rust were produced but never fully weaponised. The Soviets, who had a much larger biological weapons programme than that of the United States, also sought to develop anti-plant weapons. The United States government conducted field tests of wheat stem rust fungus in North Dakota and Florida in the 1960s. Later, the small Iraqi biological weapons programme produced more than 2 000 l of aflatoxin, most of which was placed into bombs or warheads that were never used. There is no evidence that either the plant pathogens developed in cold war programmes or the aflatoxin produced by the Iraqis was ever used against an adversary as a weapon of war. Between 1961 and 1971, the United States sprayed millions of gallons of defoliant herbicides, such as 'Agent Orange' over South Vietnamese jungles in an attempt to reduce vegetation that provided concealment to the North Vietnamese. This use of a chemical herbicide in war and its apparent toxic effects on humans, have been the subject of much controversy, many lawsuits and compensation claims for the families of some victims. With the global spread of the modern tools of biotechnology and their application, it is critical that scientists work together across national boundaries to educate and create awareness across all scientific communities, fostering a culture of responsibility and stewardship. However, legal prohibitions are not enough in this age of asymmetric warfare; we also must prevent intentional introduction of disease by subnational groups and even individuals. Prevention of intentional outbreaks may be very difficult, but we must attempt to prevent them by dealing with 'intent' at its source.

Preventing natural incidents

Preventing the introduction or spread of disease or infestation is often more efficient than mounting response or recovery operations. Among the human population, preventive medicine is cost-effective but, because it requires individual and group behaviour modification, it is never fully exploited. For years, the lives and health of humans and animals have been improved through vaccination; for example, we have successfully eradicated the causative virus of smallpox from the globe. The animal populations of many nations are free from FMD, rinderpest and other viral diseases; prevention of reintroduction is accomplished through both technical means and government policy and practice. Traditionally, plant populations were protected with insecticides and fungicides, but it is in the plant arena that the early application of powerful tools of synthetic genomics has had the greatest impact, through the development of disease- and pest-resistant strains. Education and training can contribute significantly to the prevention of disease in all three kingdoms. Preventive medicine and proper husbandry practices, practised only by humans, can improve the health and well-being of all life and improve balance in the food chain. Lessons learned from our management of animal and plant populations and greater diligence with respect to human preventive medicine practices could significantly reduce the burden of health care in our nation.

In any disease outbreak – natural, accidental or intentional – in human, animal or plant populations or combinations thereof, early discovery and diagnosis of the disease are the most valuable interventions. Following that, situational awareness during an outbreak and the technical tools of response and recovery are essential. Following the temporal confluence of the 9/11 attacks and anthrax crimes in 2001, the United States felt a new urgency to plan and coordinate responses to bioterrorist threats. As one outcome, an impressive array of local, state and federal agencies have focused their efforts on a comprehensive response, the elements of which have also benefitted investigation of accidental disease outbreaks and response to natural disasters. The Laboratory Response Network (LRN), formed in 1999 by the Centers for Disease Control and Prevention (CDC), collaborating with the Federal Bureau of Investigation (FBI) and the Association of Public Health Laboratories, now links federal, state, and local public health laboratories with veterinary, agriculture, military, and water- and food-testing laboratories for a coordinated response to a bioterrorist event (12).

With respect to disease surveillance, the plant community has led the way in the United States by applying new telecommunications strategies. Possibly because of necessity, since there are fewer 'plant doctors' than 'human or animals doctors' to monitor disease in their respective populations, and possibly because the stationary nature of plant life makes disease monitoring somewhat more straightforward, the USDA, in conjunction with the academic community, has developed a remarkable collaborative system called the National Plant Diagnostic Network (NPDN) (www.npdn.org). The NPDN links experts in five regions across the nation to rapidly respond to the introduction or spread of new pathogens. Similar systems, although less simple, elegant or well practised, exist for animal and human disease. An eventual Department of Homeland Security (DHS) goal is to integrate all of these systems in the National Biosurveillance Integration Center (www.dhs.gov).

Just as behaviour is an element that is important in the intent to harm via biology, behavioural solutions exist in the fields of preparedness for, and response to, an attack or a natural or accidental outbreak of disease in human, animal or plant populations. Awareness training and education for physicians, veterinarians, plant pathologists, extension agents, farmers and ranchers contribute to preparedness of the first line of defence. An understanding of disease processes and outcomes in each kingdom makes the human population more resilient, as well as more willing and capable of containing an outbreak. A strong capability in microbial forensics is being developed to support response efforts, provide attribution and, perhaps, serve as a deterrent to the intentional use of biological agents against humans, animals or plants. Finally, working together on difficult health-related problems internationally, and across the scientific disciplines and agencies interested in human, animal and plant health, builds high-value networks of understanding and trust that can be important resources in times of outbreak or other crisis.

Response and recovery, following the introduction of pathogens or pests, differ across the kingdoms. Humans are given care as individuals, as long as the health care system can manage to do so, and are treated at almost any cost. In contrast, animals and plants are typically treated as populations and are often isolated and destroyed, if warranted, to stop the outbreak. The better we are prepared to prevent or respond to an outbreak, the lesser the impact. The dilemma is measuring risk – especially in the case of intentional events – and deciding what level of resources to commit to prevention, preparation and response.

The biotechnology revolution

We are in the midst of a biotechnological revolution. The rate of knowledge growth in biology and the ability to manipulate it, is growing even more rapidly than in the information revolution at the end of the last century. Synthetic genomics will change the way we define microbial life in the coming years. The convergence and resultant synergies of biotechnology and nanotechnology with the already broadly available information technologies may be as powerful as the Industrial Revolution (28). Scientists in many nations are working to engineer microbes that can provide services to mankind. The booming economies of China and India are already harnessing genetic tools widely in the context of plant research and these new tools are spreading rapidly around the globe. The power of these activities is taught at ever lower levels within our educational systems. The vast majority of research and application powered by these new technologies will be for the good of plants, animals, humans and the environment.

However, just as with tools that have come before, including fire, the wheel and gunpowder, the tools of biotechnology can also be used to harm. Just after the turn of the 21st century, in the new small world of asymmetric warfare, several intentional or serendipitous findings related to the manipulation of microbes (30) gave us pause regarding the enormous power of the biotechnologies and the potential harm that could result. The transmission and sharing of disease across species and even kingdoms will likely become more prevalent, rather than less so, for the foreseeable future. As travel and information sharing bring humans, animals and plants closer together in time and space, our ability to manipulate life forms accelerates. As the fields of biology, chemistry and physics meld, we will, of necessity, be 'living' 'One Health'. These stressors in our global society may increase the likelihood of intentional pathogen introduction.

Conclusions

Life on Earth is sustained by, and dependent upon, myriad links among its species. Humans, with their ability to think and reason, to build palaces and write poetry and travel to outer space, cannot survive without plant and animal life. As we learn more about the biology of each kingdom, we are struck by the remarkable number of mechanisms and strategies shared among kingdoms. Much can be learned from comparative studies and from research conducted by integrated teams of scientists having widely different training and backgrounds. The sooner we understand the complex trends that threaten us and release the power inherent in the integration of specialists and technologies from around the world, the better we will be able to protect, nurture and sustain our human, animal and plant populations and thus our global environment.

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