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To most people, Lyme disease is a risk of life near wooded regions. But not long ago, there was little suspicion that a tick-borne disease could be causing rashes, arthritis, and neurologic conditions. And before the isolation and characterization of the causative spirochete, there was widespread doubt that such a disease complex was real.

Why discuss emerging organisms at a forum on Lyme disease? With such a history, the annual Lyme disease conference has become a platform to discuss other suspected and recognized emerging diseases. Over the course of this 2-day conference, investigators presented recent data on West Nile encephalitis, the various forms of ehrlichiosis, and an unusual dinoflagellate that is responsible for major fish die-offs and human disease as well.

Viruses and Idiopathic Neurologic Diseases <level 1>

The West Nile virus, previously confined to Africa, Europe, and the Asian subcontinent, made its way to Northeast Queens in metropolitan New York City during the late summer of 1999. How it got there is a matter of speculation, with hypotheses running the gamut from importation (illegal or otherwise) of tropical birds, to aberrant migration of an infected bird, to human introduction via immigration of an infected individual. In a keynote presentation, Dr. W. Ian Lipkin,[1] from the Emerging Diseases Laboratory at the University of California in Irvine, provided a glimpse into the latest viral pathogen known to enter the Western Hemisphere.

Detection of the virus was made possible by current DNA technology, which permits the simultaneous display of thousands of nucleic acid sequences through polymerase chain reaction (PCR) amplification techniques.[2] These differential displays allow for recognition of conserved expression patterns, which can be isolated and subjected to further analysis, amplification, and segregation. From these data, a simple, single-stranded RNA flavivirus, distinct from the pathogen causing St. Louis encephalitis but similar to endemic West Nile virus, was identified. At the same time, over 400 cases of West Nile virus were diagnosed in Israel, with 29 fatalities. Both soft and hard-bodied ticks are known vectors for West Nile virus, and many of the bird species that tested positive for West Nile virus are natural hosts for these ticks in the United States. If current trends are predictive, it is likely that West Nile virus will become endemic to North America in the next several years.

The rapidity by which West Nile virus has spread throughout the eastern United States suggests that other viruses, as yet undetected and undefined, are involved in the pathogenesis of numerous other idiopathic diseases. Regarding encephalitis alone, 50% to 70% of cases in the United States remain idiopathic. As the technology for cloning nucleic acids of pathogens from clinical specimens continues to advance, it is believed that more of these idiopathic entities will be identified.

One such entity is Borna virus, which has been associated with hyperactivity, exaggerated startle responses, and dysfunction in cellular immunity in rat models in the acute setting, and with abnormal stereotypic motion behavior, dyskinesias, dystonia, and CNS lesions affecting dopamine regulation in chronic infection. Behavioral expression in adult rats is markedly different from that observed in infant rats exposed to Borna virus, and unlike chronic adult overexpression of dopamine, an upregulation of 5-hydroxytryptophan is found in the brains of infant rats, particularly in the hippocampus. Intriguing associations that have been ascribed to Borna virus include multiple sclerosis, amyotrophic lateral sclerosis, major depression disorder, bipolar disorder (where this organism has already been identified in select cases), schizophrenia, chronic fatigue syndrome, and panic disorder.

Viral origins are suspected in other undefined conditions, including pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) and Sydenham's chorea. It is hoped that the new technologies currently being used in clinical research will eventually allow investigators to sequence microbial, nutritional, and environmental toxin patterns in order to determine what, if any, effects these and other undefined factors have on individuals at age-specific points in time.

A Brief History <level 2>

According to Dr. John Anderson[3] from the Connecticut Agricultural Experiment Station in New Haven, the first reported human case of West Nile virus can be traced to a Ugandan woman in 1937. The first major human epidemic occurred in Israel from 1950 to 1954; the first major European outbreak was found in Romania, followed by the most recent New York and Russian outbreaks in 1999. The virus is transmitted from *Culex* mosquitoes to wild birds.

However West Nile virus arrived in North America, 62 patients were diagnosed with severe West Nile viral encephalitis in 1999, resulting in 7 fatalities.[4,5] Presenting symptoms included fever, muscle weakness, headaches, photophobia, and myalgias. Eventually, 2.6% of the population of Queens

showed serologic evidence of West Nile virus exposure. At the same time, scores of exotic bird deaths were recorded at the Bronx Zoo, and thousands of bird deaths occurred in the surrounding area. An additional 21 cases were reported in the United States in 2000: 14 from New York, 6 from New Jersey, and 1 from Connecticut, with 2 deaths. While mosquitoes in 4 states tested positive for the presence of the virus in 1999, that number had risen to 12 states plus the District of Columbia in 2000. Bird studies have demonstrated that at least 15 bird species are currently affected, and the virus has been found in several mammals, including raccoons, bats, cats, rats, and horses.

Dr. Anderson concurs that the West Nile virus in North America is here to stay. Dr. Anderson also believes that there are viral triggers to a host of diseases, such as multiple sclerosis and autism, waiting to be defined. One encouraging note from the Western United States is the tentative identification of a new virus isolate that may be responsible for up to 25% of Western encephalitis cases.

Ehrlichiosis in the Northeast United States

A number of patients appear to have atypical presentations of Lyme disease, although they are seronegative by current testing standards. Is it possible that other tick-borne diseases may be responsible for atypical presentations? A number of talks examined this issue.

Ehrlichia cause disease in both humans and domesticated animals, including dogs, horses, cattle, and deer, according to Dr. Louis Magnarelli,[6] the Vice-Director of the Connecticut Agricultural Experiment Station. Symptoms of human ehrlichiosis include fever, headaches, myalgias, and lethargy. Outbreaks generally occur in the summer, and there is usually no rash. Marked thrombocytopenia and leukopenia are characteristic, and decreases in hemoglobin have also been reported. Most importantly, like its Lyme counterpart, ehrlichiosis is a curable disease when treated with the appropriate antibiotics. *Ehrlichia chaffeensis* and *Ehrlichia phagocytophilia* are considered to be human pathogens, although the latter affects horses and cattle as well. The *Ixodes scapularis* tick of Lyme disease fame serves as the chief vector, although *E chaffeensis* has been detected in *Amblyomma americanum*, the lone star tick.

Antibodies to a 44 kDal antigen are most commonly seen in human granulocytic ehrlichiosis (HGE), and a recombinant ELISA antigen has been created for diagnostic testing.[7] Both granulocytic and monocytic forms of ehrlichiosis exist, and these entities can be differentiated on Western Blot assay by the presence of the 44 kDal band seen in HGE vs 29 kDal and 28 kDal bands observed in human monocytic ehrlichiosis (HME).

E phagocytophilia, the most prevalent *Ehrlichia* in Connecticut, is responsible for most HGE, of which there were 420 confirmed cases between 1995 and 2000 and an additional 839 suspected cases. With recent increases in the deer population, an accompanying rise in the tick population has followed, and *E chaffeensis* has been detected in 7.6% of ehrlichiosis cases in Connecticut and 11.5% of cases in Rhode Island.[8] Because Lyme disease, ehrlichiosis, and babesiosis are all tick-borne diseases, Dr. Magnarelli recommended that any individual suspected of having any one of these diseases be tested for the full northeastern triad. He also attempted to dispel the myth that ehrlichiosis is a mild disease, particularly in those patients who may be infected with concurrent Lyme disease.

Tick-Borne Diseases in the Show-Me State?

Shifting geographic locales, Dr. Edward Masters[9] described the state of tick infestation in Cape Girardeau, Missouri, as well as throughout the Midwest and parts beyond. While a tick vector triad certainly exists in the Northeast, Dr. Masters suggested that another triad probably exists in the South, made up of Lyme borreliosis, ehrlichiosis, and babesiosis, but with different tick vectors involved. The lone star tick appears to be the vector responsible for the prevalence of HME in Missouri. Patients often present with leukopenia, thrombocytopenia, and elevated liver enzymes. Unlike HGE, patients with HME often present with a petechial rash of the feet and/or thighs, but the course of disease is often much milder than HGE. And unlike the northeastern version of HGE, there is a southern version that has been linked to *Ehrlichia ewingii*.

Babesiosis appears to have its own midwestern flavor. While *Babesia divergens* is responsible for the babesiosis seen in Europe, *Babesia microti* accounts for most cases on Nantucket Island and in the East as well as the upper Midwest. One case of babesiosis in Missouri was reported in which patient serum was strongly reactive by IFA for *B divergens* with only minimal reactivity to *B microti*. This "unique" bacteria was named *Babesia* MO1, although Dr. Masters suspects that *B divergens* and MO1 are really the same.

Lyme disease in the Midwest also differs from the northeastern version, and has been dubbed Masters' disease (among other names) by local wags. Patients are usually bitten by lone star ticks and often recall the particularly distinctive markings of that tick when describing it to their physicians.[10,11] The view under the microscope usually shows a lymphocytic infiltrate, compared to the plasmacytic infiltrate more characteristic of traditional Lyme disease. The incidence of EM lesions may be greater, and there may be more central clearing in EM lesions. Seropositivity, as defined by CDC guidelines, tends to be lower. Nevertheless, Dr. Masters indicated that "absence of proof IS NOT proof of absence," and so he treats his patients accordingly.

Bartonella: More Than Cat-Scratch Disease?

In her practice at Mountainside Hospital in New Jersey, Dr. Lesley Fein[12] has seen many cases of co-infection with tick-borne illnesses and *Bartonella*. This raised the question of whether the same tick vector, *Ixodes scapularis*, is responsible for dual transmission. Traditionally, *Bartonella henselae*, a gram-negative bacteria, is transferred from animal to human via cat scratch, hence its association with cat-scratch fever.

Patients infected with *Bartonella* first develop a papule, which eventually becomes vesicular and crusting. Regional lymphadenopathy is almost always present, and biopsy usually demonstrates a granuloma, from which the bacteria may be isolated. The incidence of neurologic involvement in a handful of patients -- including neuroretinitis, encephalopathy, radiculopathy, peripheral neuropathy, facial palsy, ataxia, myelopathy (with transverse myelitis), and positive brain biopsy for *B henselae* in one immunocompromised host -- led her to wonder whether co-infection with *B burgdorferi* and *Bartonella* were responsible.

To demonstrate the frequency of both *B henselae* and *B burgdorferi* in animals and ticks, Dr. Fein reviewed the medical literature. Studies in domestic cattle, cats, rodents, and deer have shown a bacteremia rate for *B henselae* ranging from 50% to 95%.[13] Cats are positive for *B henselae* in 89% of cases, and even fleas test positive 34% of the time. In select cultures of mice, 75% have been positive for *B burgdorferi*, while 10% have been positive for *B henselae*. Ticks in The Netherlands have been shown to be positive for *B henselae* by PCR analysis in 70% of cases, while ticks in California (*Ixodes pacificus*) have just recently been shown by PCR analysis to carry *B henselae* in 19% of those tested.

One third of all New Jersey ticks tested have been positive for *B henselae*. When the backyards of these tick-bitten patients who presented with severe neurologic disease were tested, *B henselae* was found. Most of these patients did not respond to conventional antibiotic treatment, and the case was made in the follow-up question period that patients resistant to treatment for Lyme disease may potentially be infected with *Bartonella* instead, or co-infected with both *B burgdorferi* and *B henselae*. An intriguing question...but one that cannot be answered from the data currently available.

Dead Fish, Toxic Cultures, and Politics

Pfiesteria piscicida, a primitive dinoflagellate, has been responsible for the deaths of millions of fish in eastern seaboard estuaries, according to Dr. JoAnn Burkholder,[14,15] Director of the Center for Applied Aquatic Biology in North Carolina. She has also shown that this microorganism can affect human health, in both acute and chronic ways. These health problems include visual changes; sleep disorders; erratic behavior; nausea; vomiting; respiratory disorders; central, peripheral, and autonomic nervous system dysfunction; cognitive impairment; and immunocompromise.

Dr. Burkholder started this work in the early 1990s in the North Carolina Albemarle-Pamlico estuary, the second largest estuary in the United States (after Chesapeake Bay), and the most important fishing hatchery in the United States. Beginning with several unexplained mass fish deaths in the 1980s, *Pfiesteria* was finally identified as the etiologic agent in 1991. The role that nutrient pollutants (farm and human sewage) played in the pathogenesis of these outbreaks was defined in 1992. *Pfiesteria*'s capacity to emit toxins when stimulated by secretions from living fish was also elucidated.

The effects of *Pfiesteria* on human health were first reported in 1995.[16] Ten individuals working in close proximity to *Pfiesteria* cultures in laboratory settings contracted symptoms after direct contact with culture water or after inhalation of aerosolized water from tank aeration systems. As described before, symptoms ranged from acute narcosis, eye irritation, respiratory distress, stomach cramps, and vomiting, to chronic skin ulcerations, cognitive impairment, and Alzheimer's-like short-term memory loss. Once contact with *Pfiesteria* was discontinued, these symptoms reversed over the course of several months, although peripheral nerve dysfunction and immunosuppression tended to linger for years. Anecdotal reports from individuals known to frequent these natural estuaries support these laboratory findings.[17,18]

The process of identifying the specific nature of *Pfiesteria*'s toxic secretions has been slow. Dr. Burkholder states that the delays are largely due to political forces that have sought to deny the existence of a *Pfiesteria* epidemic. With pressure from the North Carolina tourist and seafood industries, several regional health agents worked to keep this information from public notice.

According to Dr. Burkholder, the Centers for Disease Control and Prevention (CDC) launched its own investigative efforts that initially played into the hands of those who opposed public disclosure and directed funding to areas where no *Pfiesteria* outbreaks had ever been recorded. Eventually, the CDC's review panel received information that supported the findings of Burkholder and associates. Shortly thereafter, in October 2000, the review panel concluded that a health hazard existed. Unfortunately, the CDC specified that further funding would be restricted to the Pamlico estuary, where no *Pfiesteria* outbreak has occurred in several years. Nevertheless, the CDC's endorsement led to the allocation of $220 million in funding from the US Department of Agriculture (USDA) for elimination of nutrient pollution by North Carolina farmers.

As Dr. Burkholder sees it, economic forces first denied, then sought to bury data that could have a negative impact on the financial well-being of special interests, similar to the early experience with Lyme disease. Only when the scientific community uses its data to support individuals adversely affected by specific disease processes and strengthens its position with the help of public advocacy forums like the Sheridan Group can health policy change come to pass.

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