Introduction: Human Enteric Caliciviruses—An Emerging Pathogen Whose Time Has Come

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In 1972, the “Norwalk agent” was discovered in fecal specimens collected during the investigation of an outbreak of gastroenteritis at an elementary school in Norwalk, Ohio [1, 2]. While this was heralded as the discovery of the first virus specifically associated with gastroenteritis, research progressed slowly and the role of the Norwalk agent as an important pathogen remained in question because of the difficulty in detecting the virus. The virus was rarely seen by electron microscopy (EM), it could not be amplified in cell culture or in animal models, and many morphologically similar agents, referred to as either “small round structured viruses” (SRSVs) or “classic human caliciviruses,” were antigenically distinct and clearly different from the prototype Norwalk strain [3]. These viruses had been designated loosely by the location where each strain was detected (e.g., Hawaii, Snow Mountain, Sapporo, Taunton). Some immune diagnostics were developed on the basis of virus and antibody prepared from specimens collected from human volunteers, but these tests were of limited value outside of the research community.

In the early 1990s, the cloning and sequencing of the Norwalk and Southampton viruses revolutionized the study of the human caliciviruses [4, 5]. Unlocking the genomic organization of this ill-defined group of viruses led immediately to the development of sensitive molecular diagnostics (e.g., reverse transcription–polymerase chain reaction, probes) that resulted in studies to better understand the epidemiology of these viruses [6, 7]. On the basis of their sequences, these viruses have now been placed into 2 provisionally named genera of the family Caliciviridae: “Norwalk-like viruses” (NLVs) and “Sapporo-like viruses” (SLVs) [8].

In this classification, the viruses previously referred to as SRSVs are largely assigned to NLVs, but classic human caliciviruses fall into both the NLVs and the SLVs [9, 10]. With the new diagnostics, NLVs that had rarely been seen by EM of fecal samples from patients with acute gastroenteritis now emerged as the most common pathogens identified in outbreaks of gastroenteritis in those countries where a diagnosis was specifically sought (i.e., United States [11], United Kingdom [12], Japan [13], The Netherlands [14], and Australia [15]). Furthermore, outbreaks that in the past might have been considered small and focal could now be linked nationally and internationally by an identical sequence of their infecting strain [16–18]. Some of these outbreaks have now been traced back to fecally contaminated foods and water in which a virus with the same sequence as the outbreak strain could be identified, confirming its causal link and opening the way to screen foods and water for evidence of viral contamination [19–21].

Calicivirus infections as measured by antibody prevalence are nearly universal in children <5 years of age, but recently, with the application of new detection methods, these viruses have been identified as frequently as rotavirus in fecal specimens of Finnish children with diarrhea [22, 23]. All these breakthroughs and advances have occurred in the absence of a simple, routine, sensitive assay for the detection of human caliciviruses in fecal specimens, a method to cultivate virus, or an animal model (other than a human model) to study pathogenesis and immunity.

This supplement provides key presentations from a meeting held in Atlanta (29–31 March 1999) to review recent advances in our understanding of the human enteric caliciviruses. Initially, five government groups in the United States, each having a different focus on and special interest in human caliciviruses, agreed to participate. These five groups included the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the US Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the US military.

CDC, which investigated the original outbreaks due to Norwalk, Hawaii, and Snow Mountain viruses, provides extensive epidemic support to many states that investigate thousands of outbreaks of gastroenteritis each year. The majority of these outbreak cases currently go without an etiologic diagnosis, although most are now believed to be due to NLVs.

For NIH, the caliciviruses are among the growing number of emerging pathogens whose full role in human health and disease has yet to be determined. In fact, the Norwalk virus was discovered on the NIH campus by Albert Z. Kapikian in 1972.

The FDA has traced outbreaks of calicivirus gastroenteritis to foods contaminated at their source and to foods contaminated by food handlers. This has raised questions about food...
hygiene practices, contamination screening, and the exclusion of infected food handlers from work. Of note, the original cloning and sequencing of the Norwalk virus by Jiang et al. [4] was funded by an FDA grant.

For the EPA, Norwalk virus has long posed a problem for community water supplies, since outbreaks have repeatedly been traced to contaminated water sources and recreational water. The inoculum required to cause disease is so small that a little contamination can go a long way, and the virus can pass through simple filters and remain infectious despite routine levels of chlorine [24].

Finally, the military must continually address issues that affect the health of soldiers in combat. Epidemics due to NLVs have crippled aircraft carrier personnel and were the single most common cause of disability of American troops deployed in the Persian Gulf during Operation Desert Shield [25, 26]. Indeed, it is a rare event when five branches of government come together to consider the importance of a single family of viruses and unite to develop a common strategy for their study, control, and prevention.

As indicated by the workshop attendance of more than 100 participants from 18 countries, the calicivirus research community is clearly international, and some of the most interesting results were reported by those working abroad. For example, the British published the first complete sequence of a human calicivirus (i.e., the Southampton agent), conducted national surveillance for SRSVs at many EM laboratories, and developed a number of new diagnostics. The Dutch were the first to apply molecular methods on a national scale and to examine the molecular epidemiology of the caliciviruses in their own country. The Japanese discovered the Sapporo agent, the prototype virus for a distinct genus of the family Caliciviridae, and they first introduced molecular testing for NLVs in many pre-fectural laboratories throughout the country that now regularly report surveillance of these outbreaks. Many other groups in Australia, Sweden, France, Finland, and Italy also have made important contributions to the field. In addition, a report of a multinational outbreak of gastroenteritis associated with febrally contaminated raspberries from Slovenia demonstrated that the problems of calicivirus-related disease are not confined to individual nations and that the new molecular diagnostics have the power to link many focal outbreaks to one contaminated food source.

The papers from this conference describe the latest advances in the field, from the first studies of the molecular epidemiology of the caliciviruses to new research on the molecular structure, virus organization, and diagnostics of the caliciviruses and to applications of these insights to the prevention of disease. Many challenges remain to be addressed, including understanding each of the reading frames of the virus and identifying reasons for the genetic diversity among caliciviruses, discovering a method to grow the virus and examine it in an animal model, and determining how much of the currently undiagnosed gastroenteritis can be attributed to this agent. Meanwhile, the field has been revitalized with new diagnostic tools and insights that, when shared and applied, can expedite improvements in the public’s health. A simple, sensitive, routine diagnostic test is still needed, but with new laboratory tools becoming available, this goal is now within our grasp. The editors hope that this supplement will provide a useful reference to those who wish to extend the current understanding of these important agents of gastroenteritis in humans.

References

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