

## Commentary: McIntosh K, Chao RK, Krause HE, Wasil R, Mocega HE, Mufson MA. Coronavirus Infection in Acute Lower Respiratory Tract Disease of Infants. *J Infect Dis* 1974;130:502–7.

### Kenneth McIntosh

Division of Infectious Diseases, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts

The 1974 article by my colleagues and me describing studies of coronavirus infection in hospitalized infants with acute lower respiratory–tract disease (LRTD) [1] takes on a particular interest in light of the 2002–2003 epidemic of severe acute respiratory syndrome (SARS) coronavirus infections, with the wider perspective provided by that event on emerging epidemics, acute respiratory infections in general, human coronaviruses, and viruses that appear to have jumped barriers between species. The study published in *The Journal of Infectious Diseases* described a collaboration between our group in Denver (pediatric virologists familiar with the diagnosis and study of coronaviruses) and Maurice Mufson and his colleagues who, at the time, were working in the pediatric wards of Cook County Hospital in Chicago. The objective of the study was to investigate the role that coronaviruses might play in LRTDs in hospitalized infants in an urban environment. The serosurvey we conducted was a supplement to a previous, more-extensive study at Cook County Hospital of traditional respiratory viruses and *Mycoplasma pneumoniae* conducted by Dr. Mufson and his colleagues [2]. Both studies used serum and respiratory samples obtained from infants <18 months of age hospitalized from 1967 to 1970.

At that time, the known human coronaviruses comprised several viruses recovered from the respiratory tracts of patients with colds. The first human corona-

virus described was isolated from a boy at a boarding school in England, was passaged in human embryonic tracheal organ cultures, and was initially detected by the capacity of culture fluids to produce colds in volunteers at the Common Cold Research Center in Salisbury, England [3]. This extraordinarily cumbersome culture system (organ cultures for viral growth and colds induced in volunteers to detect virus in culture) was used to show that the virus was ether sensitive but was not related to other known ether-sensitive respiratory viruses, such as influenza virus, parainfluenza virus, or respiratory syncytial virus. David Tyrrell and his colleagues isolated this virus and described it, and he and June Almeida, an electron microscopist, first examined these infectious fluids and saw particles that looked like avian infectious bronchitis virus [4]. Although coronaviruses were not yet named, they were first characterized and separated from other virus families at that time.

The human coronaviruses fell into 2 broad groups: group I coronaviruses, which are biologically and antigenically related to strain 229E, described in 1966 by Dorothy Hamre at the University of Chicago [5], and group II coronaviruses, which are related to strain OC43, described by researchers at Robert Chanock's laboratory at the National Institutes of Health [6, 7]. Group I human coronaviruses grew from clinical specimens in tissue culture, but only with some difficulty. Group II human coronaviruses grew only in organ culture of human embryonic trachea, and some of them were antigenically related to mouse hepatitis virus (MHV) and grew in the brains of suckling mice [6].

During the 1960s, both 229E-like and OC43-like viruses had been linked clearly only to minor upper respiratory–tract diseases. All the known human corona-

Reprints or correspondence: Dr. Kenneth McIntosh, Div. of Infectious Diseases, Children's Hospital Boston, 300 Longwood Ave., Enders 609, Boston, MA 02115 (kenneth.mcintosh@tch.harvard.edu).

**The Journal of Infectious Diseases** 2004;190:1033–41

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0022-1899/2004/19005-0024\$15.00

virus strains were administered to adult volunteers in Salisbury, England, and were shown to be pathogenic, albeit mildly so [3, 8, 9]. In contrast, we had been unsuccessful in all our earlier serologic studies in establishing a connection between coronaviruses and LRTDs in infants [10].

The tentative conclusion of the 1974 article published in *The Journal of Infectious Diseases* [1] was a linking of coronaviruses (both 229E and OC43) with ~8% of cases of LRTD in hospitalized infants <18 months of age, as found by both increases in antibody levels and isolation of 229E-like viruses from 2 infants with pneumonia. The article is interesting from many perspectives.

First, one of the antigens used in the complement-fixation serologic tests was a mixture of 4 strains of MHV. This procedure was done because MHV had already been shown to be closely related to OC43 and because there was a suspicion that there were other animal-related coronaviruses that caused disease in human beings and were waiting to be discovered. In fact, no infections were identified in which there were no increases in antibody to the 2 human coronavirus strains.

Second, even with the addition of coronavirus infections, there remained many illnesses in the epidemiologic survey without an assignable microbial cause. Many of those illnesses were probably bacterial pneumonias. We still have a dim picture of the spectrum of etiologies in bacterial pneumonia of infants, but it is suspected, on the basis of data in studies that include the use of serologic methods for the detection of *Streptococcus pneumoniae* [11] and of epidemiologic surveys of infants receiving the conjugated pneumococcal vaccine [12], that many cases of pneumonia are bacterial in origin, including some that would be described as “atypical” (and, therefore, previously considered to be viral, chlamydial, or mycoplasmal). Other illnesses may have been infections with human metapneumovirus, which recently has been described in multiple studies showing its involvement in LRTDs in infants during winter epidemics [13, 14]. Still other illnesses may have been infections with rhinovirus, since rhinovirus is a common pathogen with a spectrum of disease similar to that of the traditional human coronaviruses. The epidemiology of rhinovirus infections is only now coming into focus, because of the application of polymerase chain reaction (PCR) technology to their diagnosis [11].

Third, the difficulty of working with human coronaviruses at that time is obvious from the tone of the article [1]. During the 1960s and 1970s, the identification of coronaviruses in clinical samples was a formidable task that required intensive attention to the welfare of tissue cultures over the course of 3 or 4 weeks and the ability to detect subtle cytopathic effects on a background of gradually dying cell monolayers. It was, incidentally, with skills like this that rubella virus [15, 16], cytomegalovirus [17, 18], varicella virus [19], and numerous other viruses were first discovered. In this respect, there is a

striking contrast with the SARS coronavirus, which appears to grow quite readily in Vero cell tissue culture [20], but even traditional group I and II human coronaviruses (those related to OC43 and 229E) are easier to detect now because of the application of PCR to clinical samples [21], and the spectrum of disease associated with genetically related strains has become clearer over the past decade.

Fourth, the tentative nature of the etiologic connection between 229E-like coronaviruses and LRTD is very clearly stated in this article [1]. With the perspective of time, a role for traditional human coronaviruses in pneumonia of children seems easier to accept, largely because, over the years, other researchers have linked coronaviruses with a small proportion of more-severe respiratory illness in various hosts: LRTDs in young adults [22], exacerbations of asthma of adults and children [23, 24], acute decompensation of very premature infants [25, 26], pneumonia in the immunocompromised host [27], extensive respiratory symptoms in adults with chronic bronchitis, and hospitalizations and deaths due to pneumonia in frail elderly subjects [28–30]. Nevertheless, these viruses, although clearly possessing some pathogenicity, do not generally produce severe illness. In this respect, they are totally different from the SARS coronavirus, which is a different sort of pathogen altogether. Moreover, many animal coronaviruses are also entirely different pathogens: some of them, such as avian infectious bronchitis virus, transmissible gastroenteritis of swine, and feline peritonitis virus, to name a few, cause major diseases in animals, and SARS coronavirus shares more features in common with them than with the illnesses caused by traditional human coronaviruses. The results described in the 1974 article in *The Journal of Infectious Diseases* [1] are an example of the severe end of the disease spectrum associated with a virus group of limited pathogenicity.

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