Bronchiolitis and asthma: Possible common pathogenetic pathways

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A discussion of possible mechanisms for virus-induced wheezing in normal and asthmatic children is presented. Presently attractive theories for immune injury in viral bronchiolitis include those which depend on pathology induced by types 1, 3, and 4 of Gell and Coombs. The continuum of viral bronchiolitis with virus-induced wheezing in young children who are labeled "asthmatic" argues for some common mechanism of bronchiolar obstruction.

Some concept of the viruses which infect the human respiratory tract is essential to a full understanding of chronic and recurrent pulmonary disease. The respiratory viruses represent to many clinicians a confusing array, a heterogeneous group of barely distinguishable individual agents which most physicians grudgingly respect as one of the permanent curses of our species, and to which they grant little recognition beyond an occasional reference to "that thing that is going around this month."

In fact, however, an enormous body of knowledge has accumulated during the past half-century about the nature of these viruses, their epidemiology, and their importance in human disease. This knowledge has accrued from the classical work of Thomas Francis, Sir Charles Stuart-Harris, Robert Chanock, Robert Huebner, Sir Christopher Andrewes, David Tyrrell, and others and from the lesser but not unimportant work of a large number of university-based virologists. It has been the subject of an excellent recent review.[1] What we understand little about, however, is perhaps the most important and the most interesting aspect of the entire subject: how they cause illness, i.e., pathogenetic mechanisms of respiratory tract disease. This gap in our knowledge extends, for most of the respiratory viruses, to a lack of practical knowledge of how to treat and prevent them. These are difficult problems. I began by saying that a knowledge of respiratory virology was necessary for a chest physician or allergist. The corollary to this message is the conviction that to understand fully the pathogenesis of viral respiratory disease, the virologist must have an understanding of chest disease, allergy, and immunology. It is this common

TABLE I. Respiratory syndromes and their associated etiologic agents

Syndrome	Microbial agents associated		
	Most often	Moderately often	Occasionally*
Common cold	Rhinovirus	Coronavirus	Enterovirus; influenza; parainfluenza
Pharyngitis	Group A streptococcus	EB virus (infectious mononucleosis); adenovirus	Coronavirus
Croup (subglottic)	Parainfluenza virus 1	Influenza A	Parainfluenza virus 2; RSV
Pneumonia	RSV (under 5 yr); Mycoplasma pneumoniae (5-15 yr)	Parainfluenza virus 3	Influenza A or B; adenovirus
Bronchiolitis	RSV	Parainfluenza virus 3	Influenza

*This column is by no means complete, since many organisms occasionally produce respiratory disease.

TABLE II. Effect of respiratory viruses on ciliated respiratory epithelium

Very destructive	Influenza virus (A and B) Herpes simplex virus Some enteroviruses (Echo)
Moderately destructive	Parainfluenza viruses Some rhinoviruses
Minimally destructive	Respiratory syncytial virus Some rhinoviruses
Not destructive	Coronaviruses Some rhinoviruses

pathway which I wish to speak about, and in particular the possible relationship of bronchiolitis to asthma.

First of all let us review briefly the respiratory viruses and the diseases with which they are associated. In Table I is a list of the most prominent respiratory syndromes and the viruses with which they have been associated. One of the axioms of respiratory virology is that all the viruses can cause all the syndromes, but there is a predominance of one or two viruses in each identifiable syndrome, which is pointed out in the table and which helps make some sense out of the nonsense.

At the cellular level, respiratory viruses have three major known effects on cells: they can destroy the cell, liberating more of their kind; they can fuse the cell with its neighbors, often destroying it at the same time; and they can grow in the infected cell without destroying it, but probably producing certain changes in its metabolism and its surface antigens. Respiratory viruses are, as far as we know, not oncogenic in human cells.

At a level of organized tissue, the effects of respiratory viruses on the respiratory epithelium can be examined during infection of organ cultures (Table II).[2, 3] In this system we are examining primarily the extent to which viruses destroy epithelial cells. All known respiratory viruses grow in epithelial

cells and most cause some destruction. Influenza virus is the most consistently destructive, followed by parainfluenza viruses and RSV, with some rhinoviruses and coronaviruses at the bottom.[2-4]

Projecting the in vivo pathogenicity of viruses, however, from knowledge of their effects on cells, in either tissue or organ culture, is difficult. If ability to destroy respiratory epithelium were the only factor in the pathogenesis of respiratory tract disease, then we would be able to predict clinical disease accurately from in vitro activity, and viral respiratory disease would be one continuum from the mild URI to devastating pneumonia. In fact, in vitro activity only partially determines virulence, and distinct syndromes exist, such as croup and bronchiolitis, which do not fit easily into a continuum of respiratory disease.

Thus, further characteristics of respiratory virus infection must be considered. At least two come to mind: the affinity of a particular virus for a particular part of the respiratory epithelium, and the host response, immunologic and other, to virus infection. The final disease pattern is a composite of these: the destructive effect of the virus at the cellular level, the tissue affinity of the virus, and the host response. Thus, although RSV is one of the least destructive of the group in vitro, it causes the most childhood disease in vivo. Apparently an affinity for bronchiolar epithelium and a capacity to sneak past the protective carrier of maternally transmitted serum antibody join with its lesser cellular destructive effects in producing major respiratory disease in infancy. In addition, the host often fails to respond with a satisfactorily protective immune response, and reinfection is common.[5]

The particular viral syndrome which is the focus of this talk, and which I see as a link between viral infection and asthma, is bronchiolitis. Clinicians who care for small children all know what this means: an acute illness characterized by profuse rhinorrhea, cough, dyspnea, and wheeze. Fever may or may not be a part of the picture. Cyanosis often is. On x-ray examination, there is hyperexpansion, occasionally atelectasis, and often a slight bilateral perihilar infiltrate. The term bronchiolitis is usually reserved for this syndrome when it occurs in children under 12 mo. Over this age it is often called wheezy bronchitis, asthmatoid bronchitis, or sometimes just asthma. The disease at various ages of childhood nevertheless forms a continuum, and there is no precise age where one can point to a change from bronchiolitis to something else.

Bronchiolitis is, in an overwhelming proportion of cases, a viral disease. It is usually caused by RSV (in which case it is epidemic in the winter months) but may be the result of infection by any of the respiratory viruses. There is a general agreement that, over all, the obstructive component does not respond to either epinephrine or corticosteroids.[6-8] Despite this dictum, it should be said that every pediatrician has seen the 3-mo-old wheezing child in the midst of the winter respiratory season whose airway obstruction clears dramatically with epinephrine. Most children who contract bronchiolitis do not have another episode of wheezing, but many do. When they do, it tends, at least in infants, to be with a subsequent viral infection.

The pathogenetic mechanisms in bronchiolitis are obscure, but there has been

no dearth of hypotheses. First, it should be said that there exists a relatively simple physiologic reason for infants to develop bronchiolar obstruction during airway infection. Infantile bronchioles, by virtue of their small size, are likely to become obstructed in response to peribronchiolar swelling, epithelial proliferation, and excessive mucus secretion.[9] According to this theory, the tropism of RSV and other infantile respiratory viruses for the epithelial cells of the small bronchioles would explain the tendency of these viruses to produce bronchiolitis. Pneumonia, on the other hand, could be explained by the capacity of some viruses to penetrate the epithelial barrier and cause inflammation in the interstitium.[10]

Nevertheless, four observations have suggested the possibility of immune injury as contributory to the pathogenesis of bronchiolitis. First, the age incidence of bronchiolitis is highest in the first 3 mo of life, a time when placentally transmitted anti-RSV IgG is universally present in the serum.[11] Second, attempts to immunize against RSV infection with a highly antigenic, formalin-inactivated, parenterally administered vaccine led to the occurrence of severe bronchiolitis in recipients upon subsequent exposure to wild RSV.[12-15] The response of vaccinees to natural RSV infection was reminiscent of the response of killed measles virus vaccines to natural measles virus infection. In the latter instance the term "atypical" measles was coined to describe a disease which resembled acute serum sickness more than true measles. The disease in the RSV vaccinees was "atypical" in that the children were for the most part beyond the age when bronchiolitis occurs and in that many cases were unusually severe. In other respects, however, this postvaccine bronchiolitis was similar to the natural disease.

Third, autopsy studies of bronchiolitis deaths in England showed the coexistence of both RSV antigens and IgG in the bronchiolar walls, along with an extensive inflammatory infiltrate.[16] Immunoglobulins were not, on the other hand, found in the lungs of infants dying with the histologic picture of pneumonia, although viral antigen was present in abundance. P. S. Gardner, who performed the studies, hypothesized that a "sensitizing" infection might have occurred previous to the bronchiolitis which led to hyperreaction to reinfection.

And finally, the clinical continuum of infant bronchiolitis and childhood asthma has suggested to many a common pathogenetic mechanism and the possibility that reaginic antibody might play some role in the virus-induced obstructive airway disease.[17]

Previous workers have used these four circumstances in the natural history of bronchiolitis to assign various mechanisms of immune injury to the disease pathogenesis. The presence of bronchiolitis during a time when maternal antibody is present and the severe nature of the disease in children with high serum antibody following vaccine implied to some investigators an Arthus-like (Gell and Coombs type 3) injury.[11] The resemblance of bronchiolitis to asthma implied a type 1 injury.[17] And Fulginiti and others[12] implicated a type 4 (delayed hypersensitivity) reaction in postvaccine RSV bronchiolitis because

of the many analogies between "atypical" postvaccine RSV illness and "atypical" measles.

Attempts to extend these observations and confirm them with more penetrating investigations have been, in general, unsuccessful. Immunologic injury due to maternal IgG in the pathogenesis of infant obstructive airway disease has not been proved. Acute sera from bronchiolitic infants contain no more antibody to RSV than those from infants with RSV rhinorrhea without lower tract involvement, children with RSV pneumonia, or control children,[18] and severity of disease is not apparently related to the level of complement-fixing antibody in acute sera.[19] Moreover, complement levels during acute bronchiolitis are normal, implying that a true Arthus-type reaction is not in effect.[20]

Likewise, attempts to demonstrate a "sensitizing" infection preceding bronchiolitis have been only partially successful. Gardner noted that RSV infection in the first few weeks of age tended to be less severe than it was later[21] and others have also pointed to this apparent sparing of children in the first month of life.[18] This observation has been cited as evidence in favor of a sensitizing infection. It has likewise been possible to measure secretory antibody to RSV in nasal aspirates from some children at the onset of hospitalized RSV disease.[22] On the other hand, analysis of RSV epidemics points to the coincidence in time of the peak incidence of mild RSV disease, pneumonia, and bronchiolitis,[23] an epidemiologic observation which tends to argue against an early mild infection followed by a later severe one.

To examine the possibility that reaginic mechanisms are important in bronchiolitis, a number of workers have measured IgE levels in children with bronchiolitis. One group found that these levels were normal in epidemic (probably RSV-caused) bronchiolitis but significantly elevated in sporadic bronchiolitis.[24] There was no difference in age between the two groups. Unfortunately, viral studies were not performed so that no statement can be made about the role of infection in these epidemiologically different episodes of wheezing. Swedish investigators discovered that IgE levels were elevated in 21 of 72 children with "asthmatoid bronchitis" (a syndrome separated by these workers from bronchiolitis on the basis of severity and age), with a preponderance in the group who had wheezed before.[25]

Thus, the pathogenesis of viral bronchiolitis remains a mystery. The prognosis of the disease, on the other hand, is becoming clearer. A certain proportion of children, varying from 30% to over 50%, appears destined to wheeze again, some of them many times. The authors of many purely clinical studies have noticed this trend, but only recently have follow-up observations been correlated with virologic data. Freeman and Todd[26, 27] found that children who experienced bronchiolitis with respiratory virus infection had a greater chance of developing asthma or major allergy (50%) than those who were infected without wheezing (17%). Moreover, bronchiolitis due to parainfluenza virus infection was significantly more often followed by recurrent wheezing than was bronchiolitis due to RSV or adenovirus infection. Rooney and Williams[28] chose for follow-up children with bronchiolitis from whom RSV had been recovered. They found

that 56% of them wheezed again, 43% more than five times, and 34% more than 10 times.

It is thus this link between bronchiolitis and the natural history of recurrent wheezing in small children that fosters the notion that the mechanism of bronchiolitis may be related in some way to the mechanism of virus-induced (and perhaps allergen-induced as well) asthma in later life.

Further evidence for this idea comes from recent studies of viral infections in asthmatic children. Berkovitch, Millian, and Snyder[29] examined 136 asthmatic children aged 6 mo to 16 yr for evidence of viral infection during acute attacks. Although their viral recovery rate was low, serologic evidence for viral infection was frequent. The organisms seen were RSV, parainfluenza, influenza, and *Mycoplasma pneumoniae.*

At the National Jewish Hospital in Denver we set up a similar study, examining 32 young (under 6) children chronically hospitalized for recurrent obstructive airway disease.[17] Most of these children could be classified as "atopic" in spite of their young age, on the basis of family or personal history of major allergy, eosinophilia, or positive skin tests. A total of 102 viral infections were identified during 2 yr of study, 58 of which were associated with acute wheezing. This was 42% of all the wheezing attacks that occurred.

The virus responsible for the largest number of wheezing episodes was RSV. There were 25 RSV infections, none recurrent, 24 of which were associated with wheezing. Five of these attacks were severe enough to require intravenous bronchodilator therapy.

The two next most "asthmagenic" viruses were parainfluenza viruses, which as a group caused 39 infections, 20 of which were associated with wheezing, and coronaviruses, which caused 19 infections, during 13 of which acute asthma attacks occurred. It was most interesting to us that influenza A, Hong Kong strain, caused 10 infections, none of which was accompanied by wheezing. We cultured for bacteria during and in the absence of wheezing and were unable to associate any of the attacks with colonization by any particular species.

The finding that viruses were clearly associated with wheezing was corroborated in a paper by Minor and others[30] in Madison, Wis. The 13 asthmatic children they chose to follow were for the most part older than those in our group, and they were studied as clinic patients while living at home. Moreover, they specifically excluded children with allergies to food, house dust, or pets.

They found in this group of children that rhinoviruses were the agents most frequently associated with wheezing. There were 26 rhinovirus infections, 15 of which were associated with wheezing. If rhinovirus infections could be classified as "severe" (i.e., associated with fever or more than one sign or symptom), then 14 of 15 infections were accompanied by wheezing. Influenza A virus infection was much more severe in their group than in ours, and was accompanied by wheezing in six of six cases. In all, a total of 61 asthmatic episodes were seen, 24 of which (39%) were associated with infections by identifiable agents. RSV infection was not found and parainfluenza virus infections were few.

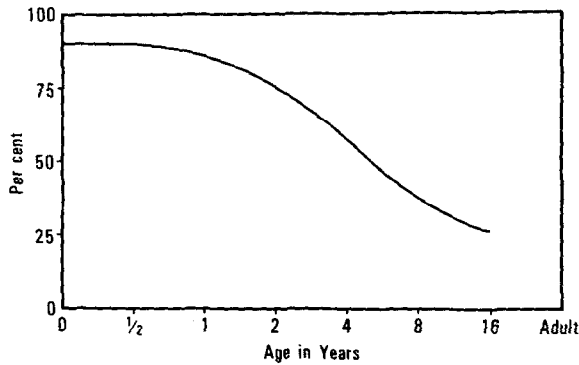Horn and Gregg[31] in England, in a study similar to that of Minor and

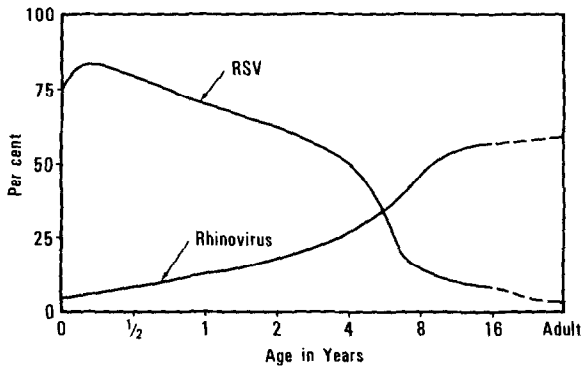**FIG. 1.** Percent of all wheezing attacks due to virus infection.

FIG. 2. Percent of acute virus-associated wheezing due to two specific agents.

associates,[30] found also that rhinoviruses were the most common viruses associated with wheezing in their group of asthmatic children. In addition, wheezing accompanied infection with parainfluenza viruses, RSV, and Coxsackie viruses.

Studies of children admitted to hospitals with acute asthmatic attacks have been somewhat contradictory. A Finnish group found virus infection in 19% of admissions for asthma, but their study was entirely serologic, and one cannot rule out the occurrence (which, in our experience, is common) of hospital-acquired infection.[32] A British study found no evidence that detectable virus infection precipitated admission to the hospital for treatment of asthma.[33] It is, however, difficult to diagnose by virus isolation alone a respiratory infection which has been present for several days before cultures are taken.

There is little doubt, then, that viruses are the precipitants of a large proportion of asthma attacks in children. The disparity between our results (no rhinovirus infections detected) and Minor's (no RSV infections) can be resolved by looking at the prevalence of all respiratory viruses and the severity of infections in different age groups. In fact, in subsequent studies of older children we have detected several rhinovirus infections, some of which were associated
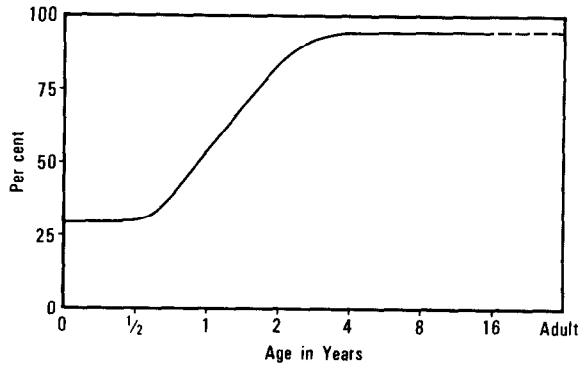
FIG. 3. Percent of children or adults with acute viral wheezing who will have recurrences.

with wheezing. It is likely that the viruses which cause the most severe infections in any given group cause the most asthma. In young children these are RSV and parainfluenza, and in older children they are rhinoviruses and influenza A. That the severity of disease, rather than the identity of the agent, is the important determining factor is corroborated by our studies of live attenuated RSV vaccines in asthmatic children.[34] These vaccines, which were either non-pathogenic or of very limited pathogenicity in normal infants and children, caused no increase in wheezing in asthmatic children, even those 2-5 yr of age, the youngest tested.

How can one synthesize the many observations detailed above into some useful concept of bronchiolitis and asthma and the possible relationship between the two? Figs. 1 to 3 summarize a number of concepts for which there are few hard corroborative data but which are consistent with the information available.

In Fig. 1 is shown a rough plot of the proportion of wheezing attacks during childhood due to viral infection. In infancy, wheezing is probably caused by viruses in the vast majority of instances. As childhood progresses, more and more children who wheeze may be said to have an allergic diathesis with wheezing triggered by viral infection or, particularly in somewhat older children, by environmental allergens. It is my feeling that, despite the contention of many clinicians to the contrary,[35, 36] bacterial infection and allergy to bacterial products rarely play a role in this triggering process during childhood.[17]

Fig. 2 gives hypothetical graphs assigning to two specific viruses a proportion of virus-induced wheezing as a function of age. If we had more data we could be more precise in the location of these two lines on the graph and we could construct similar graphs for all the respiratory viruses.

Fig. 3 addresses itself to the question of who will have recurrences of wheezing after once presenting with a virus-induced attack. The data we have from long-term follow-up of children with bronchiolitis provide us with the left-hand portion of the curve. The right-hand portion is very much open to question, since no studies have been directed at children in this age group. The rise of the curve is, however, consistent with the idea that older children who wheeze with viral infection do have family and personal histories of allergy or asthma,

that they probably possess elevated serum IgE levels, and that they will have wheezed before and will wheeze again. I intentionally avoid the terms intrinsic and extrinsic, since I find them confusing. It is highly likely, however, that when more data on the basic metabolic or immunologic defects in asthma are known, this curve can be drawn more intelligently and more accurately.

In summary, then, although the mechanisms of wheezing in bronchiolitis and asthma are not explained, it appears possible, and indeed likely, that the two diseases share, at least in some respects, common pathogenetic pathways, and that new knowledge about one disease will help in investigations of the other.

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