CLIN REV ALLERG
1983;1:5–17

Role of Viral Infections in Asthma and Allergy

Oscar L. Frick

An association between virus infections and asthmatic attacks has been recognized at least since Maimonides'[1] observation (c. 1170 A.D.), "I conclude that this disorder (asthma) starts with a common cold, especially in the rainy season, and the patient is forced to gasp for breath day and night." However, in 1918 Rackemann[2] observed that "150 cases of asthma can nearly all be divided, according to the etiology of their attacks, into . . . 'extrinsic asthma' due to inhaled antigens or 'intrinsic asthma' in which infectious agents sensitized the bronchial mucosa."

In 1962, Freeman and Todd[3] reported in a retrospective study that of 357 hospitalized children with viral respiratory infections proved by positive viral isolates on cultures, 27% wheezed during the virus infection. Especially in children under age 2, wheezing occurred in infections with respiratory syncytial virus (RSV) (52%), parainfluenza (21%), and adenoviruses (13%). In a 20-month mean follow-up, 50% of the children who wheezed with the viral infection, especially those with parainfluenza, subsequently developed asthma or other allergies, whereas this occurred in only 17% of the children who did not wheeze with the virus infection. Boesen[4] observed that, when asthmatic bronchitis occurred under age 1, later allergy occurred only rarely, whereas if it occurred between ages 1 and 3 or over 3 years, later asthma occurred in 25% and 50%, respectively. These studies suggested that early virus-induced asthmatic bronchitis was associated with later development of asthma and other allergies. Three reports in the late 1950s associated outbreaks of Asian influenza in camps with epidemics of wheezing or asthma.[5–7]

Berkovich et al.[8] associated wheezing, by serologic evidence of infection, with various respiratory viruses or *Mycoplasma* in 27 of 84 asthmatic children; they also found it almost equally in one-third of children who had influenza type A_2 or parainfluenza viruses and in one-fourth of children with *Mycoplasma pneumoniae*. Severe respiratory distress was observed more frequently during wheezing episodes associated with virus and/or *Mycoplasma* infections.

The definitive landmark studies of McIntosh et al.[9] and Minor et al.[10] in 1973 and 1974 established the association between virus infections and wheez-

From the Department of Pediatrics, University of California, San Francisco, San Francisco, California.

Send correspondence and requests for reprints to Oscar L. Frick, MD, HSW 1404A, Department of Pediatrics, University of California, San Francisco, CA 94143.

0731-8235/83/010005-13$03.00

ing attacks in asthma. McIntosh et al.[9] prospectively investigated 32 chronically hospitalized children under 5 years of age with bacterial and viral cultures and serologic studies at the onset of each of 102 acute respiratory illnesses, which averaged 3.2 infections per child. In the 2 years, 42% of acute wheezing attacks were associated with proved viral infections. At times when particular respiratory viruses were prevalent, the proportion of wheezing attacks due to infection was much higher, e.g., 85% during one winter with RSV, parainfluenza, and coronaviruses. RSV was most common in 25 of 32 (78%) children; 24 cases were associated with wheezing, 13 with lung infiltrates or atelectasis, and 17 required bronchodilators. Parainfluenza type 2 and types 3 and 1 were second, with wheezing in 12 of 32 children. In 10 children with only coronavirus OC 38-43, all had symptoms, 7 with wheezing and 3 with pneumonia. Wheezing occurred in 4 of 13 adenovirus infections. In these young children, *no* wheezing occurred with 11 influenza A_2 (Hong Kong) infections in contrast to other studies on older children and adults. Furthermore, there was no correlation of wheezing illness with infections with common gram-positive or -negative bacterial pathogens. They concluded that 42% (58/139) of episodes of wheezing in young children were associated with identifiable virus infections, predominantly RSV, parainfluenza type 2, and coronaviruses.

Subsequently, the University of Wisconsin team published studies[10–12] on the association of wheezing and virus infections in three different patient groups. First,[10] in a group of 16 school-age (3–11 years of age), nonallergic, "intrinsic" asthmatic children, two-thirds (42/61) of asthma attacks were coincident with severe respiratory infections (SRIs). Asthma occurred in 38 of 49 SRIs and mild respiratory infections in only 4 of 22. Rhinovirus infections predominated in which 15 of 26 (58%) produced both asthma and severe infection (fever and two other signs or symptoms, e.g., rhinorrhea and cough). Influenza A_2 (Hong Kong) in six children caused asthma and SRI, although in three cases other infectious agents were present. However, wheezing was present in all patients with influenza A_2HK infection. In this age group, no other viruses or bacteria precipitated asthma attacks (except one with *Haemophilus influenza).* The virus spectrum associated with asthma attacks in these school-age nonatopic children differed from that found by McIntosh et al.[9] in preschool atopic children. McIntosh et al.[9] found parainfluenza 2 but no influenza A_2HK associated with asthma attacks, whereas Minor et al.[10] found the exact converse. The latter suggested that the severe infections caused the respiratory irritation required to exacerbate asthma.

Minor et al.[11] found a greater frequency (54 versus 35) of known viral respiratory infections in the 16 asthmatic children as compared with their 15 nonasthmatic siblings ($p < 0.01$). Similarly, respiratory infections of both proved viral and unknown etiology (most probably viral) were significantly more frequent in asthmatics than in nonasthmatics (81 versus 57, $p < 0.02$), with a per subject incidence of 5.1 for asthmatics and 3.8 for nonasthmatics. The major increase in asthmatics was in symptomatic infections with rhinovirus (24 versus 11, $p < 0.01$) compared to nonasthmatics, although the difference in the asymptomatic rhinovirus incidence was not significant.

Overall, the total respiratory infection (viral and bacterial) incidence in both

groups was not statistically different; asthmatics had a lower incidence of bacterial infections than their siblings. Concurrent respiratory infections occurred in 24 instances in asthmatics and their siblings in whom the average duration of infection was 6.1 and 4.4 days, respectively. Although illnesses lasted longer in asthmatics, this difference was not significant ($p > 0.05$). Minor et al.[11] suggested that the difference in infection rate in asthmatics was due to their necessarily increased indoor life in a cold climate, resulting in longer exposures to respiratory viruses shed by other family members. This increased exposure was especially to rhinoviruses, which are likely to precipitate asthma attacks. Not mentioned was the possibility that the slow resolution of mucus plugging of the small airways after an asthmatic attack might leave the asthmatic more vulnerable to a fresh infection. Minor et al.[11] concluded that exposure of asthmatic children to individuals with respiratory infections should be minimized.

In a subsequent study by the Wisconsin group, Minor et al.[12] confirmed that both rhinoviruses and influenza A virus infections were asthmagenic. Forty-one children, aged 3–17 years, and 8 adults, aged 22–60 years, with four or more infection-induced asthmatic attacks per year were cultured during infections. Asthma occurred in 55% (71/128) of symptomatic respiratory infections; the pathogen was identified in 42 of 128 infections, 19 of which were associated with wheezing. Seven of 15 symptomatic rhinovirus infections were linked with asthma, as were 4 of 5 influenza A and 2 of 3 RSV infections. Rhinoviruses of 14 different serologic types were associated with wheezing. Although type-specific rhinovirus immunity appears to be long-lasting, the 89 known rhinovirus types provide a sufficient variety of exposure for successive wheezing attacks in asthmatics. Certain rhinovirus types may be more asthmagenic, such as type 49 in 1972, which was associated with asthma in 5 of 6 infected individuals. Although virus identification in older children and adult asthmatics was more difficult, viruses appeared to precipitate wheezing in a wide age spectrum of asthmatics.

In summary, these four studies[9–12] implicate symptomatic respiratory virus infections in triggering attacks of wheezing in asthmatic individuals. In preschool children, RSV and parainfluenza are predominant in this role, whereas in older children and adults, rhinovirus and influenza A are predominant. Occasionally, other viruses such as corona- and adenoviruses may be involved. Bacterial infections generally do not provoke wheezing, although in some asthmatics they may accompany virus infections and possibly play an as yet unexplored adjunctive role. Therefore, prophylaxis of asthma attacks involves prevention of contact between the asthmatic patient and individuals with respiratory infections.

Virus infections may play a role in the allergic sensitization process, especially in individuals genetically susceptible to the development of atopy. That asthma runs in families was known in ancient days.[1] A simple Mendelian dominant inheritance pattern was proposed by Cooke and VanderVeer,[13] who observed that if both parents were allergic, 75% of their children developed allergy, most often in their preschool years; however, if only one parent was allergic, only 50% of their children developed allergy. Today, we know that the genetics of atopy is polygenic.[14–16] The total serum immunoglobulin (Ig)E

level is concordant in monozygotic twins and usually discordant in dizygotic twins.[14] Total serum IgE is controlled by a gene not on chromosome no. 6.

Immune response (Ir) and immune suppressor (Is) genes of the histocompatibility loci (HLA) on human chromosome no. 6 appear to control responsiveness to certain allergens. Levine et al.[15] described a hayfever haplotype in seven families allergic to ragweed. One haplotype occurred in all ragweed-sensitive family members, but not all members with that haplotype were allergic. However, no member of the family who was allergic to ragweed failed to have that haplotype. In different families different haplotypes were associated with ragweed allergy. Friedhoff et al.[16] found certain positive correlations (Ir genes) of HLA type and IgE antibodies to particular pollen fractions (ragweed Ra5 with HLA-Dw2, B7; Ra3 with HLA-A2, A28) and a negative correlation (Is genes) of HLA type with other pollen allergens (Ra3 with HLA-A3, A11). In a study by Hozouri et al.,[17] monozygotic twins generally had a high concordance rate for the presence or absence of positive skin tests and a radioallergosorbent (RAST) test. This was true of monozygotic twins raised in different as well as in similar environments; this reinforces a genetic basis for atopy. Human Ir and Is genes have been associated with a response or a lack of response to certain virus infections; e.g., HLA-Dw2 individuals are poor T-cell responders to measles virus, which suggests an Is gene that may cause susceptibility to multiple sclerosis.[18] Dutch army recruits with HLA-C3 failed to develop lymphoproliferation with vaccinia after primary vaccination, suggesting Is genes or the lack of a target cell receptor for the vaccinia virus.[19] It is conceivable that certain viruses stimulate HLA-associated Ir or Is genes for certain allergens, thereby initiating the allergic sensitization process in genetically susceptible individuals.

Viral respiratory infections in children from allergic families appear to be associated temporally with the onset of allergy in our studies.[20,21] In families with two allergic parents, 24 infants were followed at 3-month intervals for symptoms or signs of allergy involving skin, nose, ears, lungs, and gastrointestinal tract, and also by in vitro immunologic tests for allergy. This test panel consisted of radioimmunoassay for total serum IgE (PRIST) and specific IgE antibodies to a panel of six common allergens in children by a RAST test, leukocyte histamine release, and lymphoproliferation with the same allergens (crude house dust, *Dermatophagoides farinae* mite, cat pelt, dog dander, ryegrass pollen, cow's milk, and soybean extracts). When it became evident that virus infections might be associated with allergic sensitization, serial serum samples were tested for virus antibodies by complement fixation tests performed by the State of California Virus Diagnostic Laboratory, Berkeley, California. The respiratory virus antibody panel consisted of influenza A, parainfluenzae 1–3, RSV, cytomegalic inclusion virus (CMV), adenovirus, and *My. pneumoniae.* Twenty-eight children from the UCSF Well-Baby Clinic served as controls and were observed at 3-month intervals for 1½ years for signs and symptoms of allergy; children with an atopic family history were excluded from this control group. No serum sampling was permitted in this group. Controls for the immunologic tests were sera from 10 nonallergic children undergoing cardiac catheterization and positive control sera from 20 children with grass pollen hayfever.

Table 1. Comparison of Clinical Symptoms of Allergy in Children from Allergy-Prone and Nonatopic Families[a]

Symptoms	Children (n = 24) from allergic families				Randomly selected children (n = 28) from well-baby clinic			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Eczema	9	10	2	21	6	1	0	7
Allergic rhinitis	4	15	1	20	6	0	0	6
Asthma	9	10	1	20	2	0	0	2
Otitis	5	6	2	13	2	1	0	3
Gastrointestinal, including colic	9	2	1	12	2	1	0	3
Total[b]				88/120				21/140
Percent positive				73%				15%

[a] $p < 0.01$.
[b] Number positive out of total possible.

A comparison of the incidence and severity of symptoms of allergy in children from allergy-prone and nonatopic families during the first 2 years of life is made in Table 1. Allergic symptoms occurred in 21 of 24 allergy-prone children and in 7 of 28 children of nonatopic families. Symptom scores for each organ system were added for each group; thus, 5 organs × 24 children in the allergy-prone group had a possible score of 120; 88 symptoms occurred, making an actual score of 73%. The control group had 21 symptoms out of a possible score of 140 (5 organs × 28 children) or 15%. Differences between the two groups in the incidence of allergic symptoms were highly significant at $p < 0.01$ using a paired t test.

Immunologic responses with common allergens in allergy-prone and control children are compared in Table 2. The infants of allergic families had about a 60% positive composite of the three immunologic tests, as compared to about 80% positive in known hayfever patients tested with grass pollen. The "normal background" was 9% positive for the three tests in nonatopic children; these mean differences between allergy-prone and nonatopic children in each test were highly significant at $p < 0.01$.

Table 2. Comparison of Immunologic Responses with Common Allergies in Allergy-Prone and "Control" Children[a]

Patient group	Immunologic test		
	RAST >1.7 e/c[b] (3 times)	WBC-HR >10%	LTT antigen >1.7 e/c
Infants of allergic families (n = 24)	78/120 (65%)	44/82 (53.7%)	48/74 (64.8%)
Allergic children with grass pollen hayfever	32/40 (80%) (n = 20)	46/50 (92%) (n = 24)	8/13 (62%) (n = 11)
Nonallergic cardiac children (n = 10)	2/18 (11%)	1/20 (5%)	1/10 (10%)

[a] Dog or cat epithelium, grass pollen mix, house dust or mites, cow's milk, and soy extract were the allergens used.
[b] e/c, experimental/control.

Table 3. Complement-Fixing Virus Antibodies in 24 Allergy-Prone Children Before and After Allergic Sensitization[a]

Virus	Parainfluenza	RSV	CMV	Total number of children
Rise in virus antibody titer	4 (2 times) 5 (4–8 times)	4 (2 times) 3 (4 times)	— 1 (2 times)	15/24
High virus antibody titer	4	1	1	6/24
Low virus antibody titer (no change)	11	16	22	3/24

[a]Values indicate number of children.

Because we observed a rise in leukocyte histamine release with antigens within a few weeks after an upper respiratory infection in several infants, we compared complement-fixing virus antibody titers of sera taken before and after the onset of the allergic symptoms. Table 3 shows that 62% of the children had rising virus antibody titers coincident with the onset of allergic sensitization; another 25% already had high virus antibody titers, not rising. Three children had low virus antibody titers, with no significant allergies and fewer upper respiratory infections. These rises in virus antibody titers were *not* different from such rises in a group of nonatopic children of comparable age. We concluded that infants from families with two allergic parents usually, but not always, developed allergic symptoms during the first year of life; the onset of symptoms coincides with demonstrable changes in immunologic tests for reactions to one or more allergens. The onset of clinical and immunologic evidence of allergy usually coincides with, or follows within weeks, an upper respiratory infection. However, we emphasize that this is just a temporal coincidence in humans and is not proof that a virus infection is responsible for allergic sensitization.

The atopic dog affords a model in which to study effects of experimental virus infection on allergic sensitization. Dogs are one of the few animal species that develop pollen allergies naturally.[22] Six hunting dogs (spaniels and retrievers) with high skin reactivity to grass and weed pollens were bred. Their puppies were used to test the effect of live virus infection on allergic sensitization processes. Half the puppies in nine litters were given routine live distemper vaccinations (a paramyxovirus) followed in 2 and 9 days by subcutaneous injections of ragweed and mixed grass pollens, 10 μg each in 2 mg alum. These injections were given at 2, 6, and 10 weeks of age. The remaining littermates served as controls and received only pollen injections followed later by the required distemper vaccinations. Canine IgE was isolated by the method of Ishizaka and Ishizaka[23] and was used to immunize rabbits. The anti-canine IgE was used in RAST assays to measure specific canine IgE antipollen antibodies. At 3 months of age, the pollen- and distemper-vaccinated puppies made significantly more antipollen antibodies than did their littermate controls. Similar studies with the same results have been made using intranasal infections of puppies with canine parainfluenza virus vaccine.

These studies suggest that certain virus infections affect the regulatory controls of IgE antibody production.

Several possible mechanisms are being studied to determine how a virus infection may induce either an allergic reaction (asthma attack) or sensitization.

Certain viral infections, for example, may affect the regulation of immune responsiveness by selectively stimulating or inhibiting regulatory T cells. Measles infections have long been known[24] to induce a state of cellular immune anergy; e.g., patients with positive skin reactions to tuberculin may temporarily lose this response during clinical measles, and this anergic state may last for weeks. Tuberculin-induced lymphoblastogenesis in such patients is impaired, although the phytohemagglutinin (PHA) response appears normal. However, children with congenital rubella syndrome failed to respond to PHA.[25] Levels of T-cell rosettes fall during acute virus infections,[26] but Reinherz et al.,[27] using monoclonal antibodies, showed that in Epstein–Barr virus (EBV) infectious mononucleosis in humans, suppressor T lymphocytes were activated and increased in number to decrease IgM antibody synthesis by B cells. On the other hand, in both CMV and EBV infectious mononucleosis, Bahna et al.[28] found an acute two- to six-fold rise in total IgE and its prolonged suppression during convalescence. Similarly, in nonallergic Army recruits, Perelmutter et al.[29] found elevated IgE in several acute respiratory virus infections and postinfection suppression for several months. Therefore, many virus infections have important effects on the regulatory mechanisms of a variety of immune responses—some effects are augmented and others are depressed, depending upon the stage of the virus infection and the immune system being observed.

An "allergic breakthrough" mechanism has been proposed by Katz[30] in which the IgE antibody system is a powerful initiator of inflammation normally controlled by IgE suppressor T cells, the "normal damping mechanism." He suggests that various stimuli or events depress the suppressor T cells, thus abrogating the damping mechanism. This permits escape of IgE helper cells to stimulate IgE B cells to make IgE antibodies. Levine and Vaz[31] showed that certain mouse strains with similar H-2 histocompatibility antigen were either "responders" or "nonresponders" for IgE production when stimulated with small microgram amounts of certain antigens in alum. Poor or nonresponders were C57B1/6 and SJL/J strains, suggesting a genetic deficiency in Ir genes. However, Chiorazzi et al.[32] demonstrated that pretreatment of SJL/J mice with low-dose irradiation (150 rads), with antilymphocyte serum, or with cyclophosphamide 7–10 days before low-dose antigen (10 μg DNP *Ascaris* in alum) immunization caused a brisk rise in IgE antibodies in this nonresponder strain. They showed by passive cell transfer experiments that suppressor T cells, which were especially sensitive to these treatments, were depleted in the mice. Then the IgE antibody response could be abrogated by transfusion of spleen cells from normal SJL/J mice by restoring suppressor T cells. More recently, Katz[33] has demonstrated soluble factors in supernatants from suppressor and helper T cells, termed suppressor (SFA) and enhancer (EFA) factors of allergy, respectively.

We propose that certain virus infections also depress the normal damping IgE suppressor T-cell controls, temporarily allowing escape of IgE helper T cells and IgE B cells to make IgE antibodies to environmental and dietary antigens.

An asthma attack may be provoked by a virus infection by a number of possible individual or combined mechanisms. These include: a) denudation of bronchial epithelium by influenza, which increases absorption of allergens and exposes rapidly alternating airway epithelial receptors (irritant or cough receptors), leading to firing with minimal stimuli; b) impairment of β-adrenergic receptor function, resulting in an autonomic nervous imbalance, which causes hyperreactivity of bronchial smooth muscles after unopposed cholinergic stimulation; c) enhanced allergic mediator release through stimulation of interferon production; and d) hypersensitivity to the virus itself, which acts as an allergen.

The simplest explanation of virus action in an allergic reaction may be the example of influenza viruses whose primary target is the ciliated respiratory epithelium.[34] These infected cells release virus particles, undergo necrosis, and slough, leaving behind only a basal layer of epithelial cells. The virus spreads from the initial infection site with progressive involvement of adjacent areas of the respiratory epithelium. The removal of this protective barrier exposes the basal cell layer to direct, facile penetration by allergens to the subepithelial mast cells. The irritant receptors are directly exposed or even sloughed, leaving exposed nerves that can also fire to cause bronchospasm with minimal stimulation.

Changes in airway resistance during virus infections were studied by Empey et al.[35] They found that, when such changes were induced by inhaled histamine in 16 normal subjects with viral upper respiratory infections, airway resistance was increased by 218 ± 55% compared to 31 ± 6% in 11 healthy control subjects. This increased bronchoconstrictive responsiveness in subjects with colds returned to normal over a 7-week period. A similar result occurred with a cough response to inhaled citric acid in subjects with colds.[35] Both responses to inhaled histamine and citric acid in these subjects could be prevented or reversed with inhaled isoproterenol or atropine. These observations were confirmed by Laitinen et al.[36] who measured baseline airway responsiveness to histamine inhalation in 12 normal subjects and then administered double-blind intranasally to half the group either live attenuated influenza A and B viruses or a placebo. Four of six virus-infected subjects had 70% increases in airway resistance on day 2 after histamine inhalation challenge, less of an increase on day 4, and none by day 9. This effect of virus infection was reversed or prevented by isoproterenol or atropine aerosols. These studies suggest an increased responsiveness of "irritant cholinergic receptors" to inhaled irritants during respiratory virus infections.

The site of the virus effect on airway reactivity was further evaluated by Little et al.,[37] who studied 37 subjects with influenza A/Victoria documented by positive cultures. Half the group was given either placebo or amantadine, the anti-influenza A virus agent, which interferes with influenza virus uncoating.[38] Diminished forced flow rates and decreased density-dependent forced flow rates while breathing a helium–oxygen mixture were observed initially

in 92% of the subjects. Seven days after the infection, the placebo group had further decreases in density dependence, whereas the amantadine-treated group had significant increases, which suggested accelerated improvement of peripheral airway dysfunction in the amantadine group. After inhalation of carbachol aerosol, 25 subjects in both groups had prolonged increases in total respiratory resistance that diminished over a 7-week period. Little et al.[37] suggested that a nonpneumonitic influenza infection had an inflammatory response mostly in the peripheral airways, with transient bronchial hyperreactivity. Amantadine arrested epithelial proliferation of virus associated with inflammation of the peripheral airways, but the virus had already initially damaged airway epithelium, causing bronchial hyperirritability that was not ameliorated by amantadine therapy. Little et al.[37] concluded that bronchial hyperreactivity was common and prolonged during the course of nonpneumonitic influenza infections in normal individuals.

Diminution of bronchial β-adrenergic responsiveness has been implicated during viral infections. Szentivanyi[39] hypothesized that asthmatic individuals have an autonomic nervous imbalance in airways due to an inherent β-adrenergic blockade. Lockey et al.[40] found support for this in asthmatics who had decreased systemic metabolic responsiveness to epinephrine and β-adrenergic agonists. The extent of decreased responses to β agonists correlated with the extent of increased cholinergic responses of the bronchi.[41] Lymphocytes from asthmatics had a lower basal level of cyclic 3′,5′-adenosine monophosphate (AMP) and a smaller increase in cyclic AMP after catecholamine stimulation than in normal subjects.[42] However, the response of asthmatics to prostaglandin (PGE_1) was normal, which indicated β-adrenergic receptor impairment rather than adenylate cyclase involvement. Thus, asthmatic individuals appear to have an impaired target cell response to β-adrenergic agonists.

Certain types of infections diminish β-adrenergic responsiveness, especially in asthmatics. In mice, *Bordetella pertussis* vaccine caused β-adrenergic blockade and hyperresponsiveness to histamine and serotonin.[43] Asthmatic subjects given killed polyvalent influenza vaccine had significantly increased bronchial responsiveness to methacholine inhalation compared to that in normal subjects; this effect lasted 3 days.[44] Lymphocytes of asthmatic individuals responded poorly to β agonists during respiratory infections.[42]

Lysosomal enzyme release from polymorphonuclear leukocytes (PMNs) has served as an in vitro model in the study of β-adrenergic responsiveness in asthmatics and during upper respiratory infections.[45] PMNs ingested complement-activated zymosan particles, which caused lysosomal but not cytoplasmic enzyme release; the release of lysosomal β-glucuronidase was measured. Isoproterenol and PGE_1 inhibited lysosomal enzyme release in both asthmatic and normal subjects in a dose–response manner. During an upper respiratory infection that provoked an asthma attack, the granulocyte response to isoproterenol was further decreased and paralleled the increased airway irritability. In a group of experimentally infected normal humans with rhinovirus 16, several symptomatic subjects had increased isoflow volumes ($\dot{V}_{iso}V$) or positive airway methacholine response.[46] They also had a decrease in β-adrenergic and H_2-histamine receptor responses of their granulocytes.

These observations were consistent with inhibition of lysosomal enzyme release from PMNs with isoproterenol in asthmatics; this inhibition decreased during viral infections, thus provoking an asthmatic attack.

In vitro studies on lysosomal enzyme release from PMNs from normal subjects after incubation with live influenza virus vaccines showed significantly impaired granulocyte response to isoproterenol, H_2-histamine, and PGE_1.[46] There was defective formation of cyclic AMP and inhibition of β-glucuronidase release with zymosan. Since lysosomal enzymes contributed to an inflammatory response, suppression of this release by β-adrenergics, histamine, and PGE_1 may modulate inflammation. Therefore, inhibition of this modulatory control of PMN functions during viral infections could accelerate the inflammation.

In smooth muscle preparations from the isolated airways of allergically sensitized guinea pigs, Buckner et al.[47] showed that parainfluenza 3 infection blocked the ability of a partial β-adrenergic agonist, sulfonterol, to inhibit antigen-induced muscle contractions. Tracheal and bronchial strips from ovalbumin-sensitized guinea pigs that had been infected 4 days before with parainfluenza 3 and noninfected controls were challenged in vitro with ovalbumin in the presence or absence of sulfonterol. β-Adrenergic agonists inhibit both antigen-induced tracheal and bronchial smooth muscle contraction and release of histamine and SRS-A from minced lung (mast cells). Sulfonterol, the partial β agonist, appears to stimulate only the β-adrenergic receptors on smooth muscle that inhibit its contraction and has no effect on mast cell β receptors that inhibit histamine release. Isoproterenol stimulates β receptors in both tissues. Parainfluenza 3 infection blocked only the sulfonterol stimulation of smooth muscle β receptors, leading to increased smooth muscle contraction, but did not block β receptors on mast cells and thus did not affect histamine and SRS-A release. Furthermore, increasing sulfonterol concentration overcame the virus-blocking action that suggested a competition between parainfluenza 3 virus and sulfonterol for β-adrenergic receptors. These experiments suggest that certain viruses may have an affinity only for certain autonomic receptors that alters physiologic end-organ responsiveness to various stimuli.

Lysosomal enzyme release from PMNs after in vitro incubation with live influenza viruses was compared in granulocytes from normal and asthmatic individuals.[46,48] Both groups had impaired PMN lysosomal enzyme release response in the presence of isoproterenol, histamine, and PGE_1. However, the cells of asthmatics had *no* greater impairment of enzyme release with these agonists than did those of normals.[48] There was no difference in this capacity in cells of intrinsic infectious asthmatics compared to those of allergic asthmatics or normals. However, in cells from asthmatics being treated with prednisone or when hydrocortisone was added in vitro, virus incubation did *not* impair PMN response to isoproterenol. These observations suggest that virus-associated effects on cell function occur at sites other than the β-adrenergic receptor itself and might involve intracellular metabolism; further, this inflammatory modulation capacity may be protected by corticosteroid therapy.

A third postulated effect of viruses in allergy and/or asthma is on the

effector target cells—basophils and mast cells. Ida et al.[49] demonstrated that herpesvirus (HSV-1), influenza A virus, and adeno-1 viruses, whether live or killed, markedly enhanced in vitro histamine release from leukocytes (basophils) of ragweed atopic patients with ragweed antigen E or anti-IgE serum. Interferon appeared to be the soluble factor in these experiments that caused this enhancement. Interferon inducers, poly I-C, and both purified human fibroblast and leukocyte interferons (IFN_α and IFN_β) all caused enhanced histamine release. Although the mechanism is unknown, virus infections that induce interferon may markedly enhance specific IgE-mediated atopic reactions.

Finally, specific IgE antibodies to viruses have been implicated in classic allergic reactions to such viruses. IgE antibodies to RSV were bound to RSV-infected epithelial cells in nasopharyngeal secretions of children with RSV infections; they were especially persistent in children with wheezing.[50] Subsequently, Welliver et al.[51] tested 79 children under 1 year of age with proved RSV infection for IgE antibodies to RSV and for histamine content of nasopharyngeal secretions. IgE antibodies to RSV in secretions rose significantly 14 days beyond the onset of illness, with mean titers of 20 during the first 2 weeks, to 58 by 2 months, and 90 by 3 months. More striking, however, were the differences in IgE antibodies to RSV when the children were divided into wheezing and nonwheezing groups. In both acute and convalescent stages of RSV infection the wheezing infants had significantly higher IgE anti-RSV antibody titers ($p < 0.05$) than did nonwheezing infants. The histamine content of nasopharyngeal secretions was significantly higher ($p < 0.01$) in wheezing compared to nonwheezing children. There was a highly significant correlation ($r = -0.92$, $p < 0.001$) between the peak of IgE anti-RSV antibody and the severity of illness, as determined by the degree of hypoxia. These studies suggest a possible IgE-mediated allergic response with histamine release to the RSV antigen, resulting in wheezing in children with this virus infection.

In summary, certain respiratory virus infections trigger or aggravate asthmatic attacks in both infectious and allergic asthmatic patients. Possible mechanisms for this include increased allergen absorption or exposure of irritant receptors secondary to denudation of the respiratory tract epithelial mucosa, virus-induced blockade of β-adrenergic receptors that induce bronchorelaxation, virus-induced enhancement of mediator release from basophils (and possible mast cells), and IgE antibodies to RSV (and possibly other viruses) acting as an allergen to induce an allergic reaction. Furthermore, certain virus infections have selective effects on cells (T lymphocytes and possibly macrophages) that regulate immune responsiveness, e.g., IgE antibody production that may initiate atopic sensitization to environmental and dietary antigens during a virus infection—a natural example of the allergic breakthrough phenomenon.

This work was supported by Allergic Diseases Center Grant AI 11010 and by Research Grant AI 15233, National Institute of Allergy and Infectious Disease, National Institutes of Health, United States Public Health Service.

References

1. Maimonides M: Muntner S (ed), in Treatise on Asthma. Philadelphia, Lippincott, 1963
2. Rackemann FM: A clinical study of one hundred and fifty cases of bronchial asthma. Arch Intern Med 22:252, 1918
3. Freeman GL, Todd RH: The role of allergy in viral respiratory tract infections. Am J Dis Child 104:330, 1962
4. Boesen I: Asthmatic bronchitis in children. Acta Pediatr 42:87, 1953
5. Rebhan AW: An outbreak of Asian influenza in a girl's camp. Can Med Assoc J 77:97, 1957
6. Podosin RL, Felton WL: The clinical picture of Far East influenza occurring at the Fourth National Boy Scout Jamboree. N Engl J Med 258:778, 1958
7. Quarles van Ufford WJ, Savelberg PJ: Asiatic influenza in allergic patients with bronchial asthma. Int Arch Allergy 15:189, 1959
8. Berkovich S, Millian SJ, Snyder RD: The association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. Ann Allergy 28:43, 1970
9. McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA: The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. J Pediatr 82:578, 1973
10. Minor TE, Dick EC, DeMeo AN, Ouellette JJ, Cohen M, Reed CE: Viruses as precipitants of asthmatic attacks in children. J Am Med Assoc 227:292, 1974
11. Minor TE, Baker JW, Dick EC, DeMeo AN, Ouellette JJ, Cohen M, Reed CE: Greater frequency of viral respiratory infections in asthmatic children as compared with their non-asthmatic siblings. J Pediatr 85:472, 1974
12. Minor TE, Dick EC, Baker JW, Ouellette JJ, Cohen M, Reed CE: Rhinovirus and influenza type A infections as precipitants of asthma. Am Rev Respir Dis 113:149, 1976
13. Cooke RA, VanderVeer A Jr: Human sensitization. J Immunol 1:201, 1916
14. Bazaral M, Orgel HA, Hamburger RN: Genetics of IgE and allergy: Serum IgE levels in twins. J Allergy Clin Immunol 54:288, 1974
15. Levine BB, Stember RH, Fotino M: Ragweed hayfever: Genetic control and linkage to HL-A haplotype. Science 178:1201, 1972
16. Freidhoff LR, Meyers DA, Bias WB, Chase GH, Hussain R, Marsh DG: A genetic-epidemiologic study of human immune responsiveness to allergens in an industrial population. I. Epidemiology of reported allergy and skin test positivity. Am J Med Genet 9:323, 1981
17. Hozouri K, Hanson B, Roitman-Johnson B, Walsh G, Blumenthal MN: Genetics of atopic diseases in twins raised together and apart. J Allergy Clin Immunol Suppl 69:121, 1982
18. Roitt IM: Transplantation, in Essential Immunology, 4th Ed. Oxford, Blackwell, 1980, p 289
19. deVries RP, Kreeftenberg HG, Loggen HG, van Rood JJ: *In vitro* immune responsiveness to vaccinia and HL-A. N Engl J Med 297:692, 1977
20. Frick OL, German DF, Mills J: Development of allergy in children. I. Association with virus infection. J Allergy Clin Immunol 64:228, 1979
21. Frick OL: Viral infections as triggers of allergy, in Steffen C, Ludwig H, (eds): Clinical Immunology and Allergology. Amsterdam, Elsevier-North Holland, 1981, p 283
22. Frick OL, Brooks D: IgE antibodies to pollens augmented in dogs by virus vaccines. Am J Vet Res 1982, in press.
23. Ishizaka K, Ishizaka T: Human reaginic antibodies and immunoglobulin E. J Allergy 42:330, 1968
24. Von Pirquet C: Das verhaltender Kutanen tuberculin Reaktion während der Masern. Deutsche Med Wochnschr 34:1297, 1908
25. Simons MJ, Fitzgerald MG: Rubella virus and human lymphocytes in culture. Lancet 2:937, 1968
26. Wybran J, Fudenberg HH: Thymus-derived rosette-forming cells in various human disease states. J Clin Invest 52:1026, 1973
27. Reinherz EL, O'Brien C, Rosenthal P, Schlossman SF: The cellular basis for viral-induced immunodeficiency: Analysis by monoclonal antibodies. J Immunol 125:1269, 1980
28. Bahna SL, Horwitz C, Fiala M, Heiner DC: IgE response in heterophil-positive infectious mononucleosis. J Allergy Clin Immunol 62:167, 1978

29. Perelmutter L, Phipps P, Potvin L: Viral infections and IgE levels. Ann Allergy 41:158, 1978
30. Katz D: The allergic phenotype: Manifestation of "allergic break-through" and imbalance in normal "damping" of IgE antibody production. Immunol Rev 41:77, 1978
31. Levine BB, Vaz NM. Genetic control of reagin production in mice. Fed Proc 30:4, 1971
32. Chiorazzi N, Fox DA, Katz DH: Hapten-specific IgE antibody responses in mice. VII. Conversion of IgE "non-responders" by elimination of suppressor T-cell reactivity. J Immunol. 118:48, 1977
33. Katz DH, Bargatze RF, Bogowitz CA, Katz LR: Regulation of IgE antibody production by serum molecules. VII. The IgE selective damping activity of suppressive factor of allergy (SFA) is exerted across both strain and species restriction barriers. J Immunol 124:819, 1980
34. Cate TR, Influenza viruses, in Joklik WK, Willett HP (eds): Zinsser Microbiology, 16th Ed. New York, Appleton-Century-Crofts, 1976, p 985
35. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA: Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Am Rev Respir Dis 113:131, 1976
36. Laitinen LA, Elkin RB, Empey DW, Jacobs L, Mills J, Gold WM, Nadel JA: Changes in bronchial reactivity after administration of live attenuated influenza virus. Am Rev Respir Dis 113 (Suppl):194, 1977
37. Little JW, Hall WJ, Douglas RG, Mudholkar GS, Speers DM, Patel K: Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. Am Rev Respir Dis 118:295, 1978
38. Kato N, Eggers HJ: Inhibition of uncoating of fowlpox virus by 1-adamantanamine hydrochloride. Virology 37:632, 1969
39. Szentivanyi A, The beta-adrenergic theory of the atopic abnormality in asthma. J Allergy 42:203, 1968
40. Lockey SD Jr, Glennon, JD, Reed CE: Comparison of some metabolic responses in normal and asthmatic subjects to epinephrine and glucagon. J Allergy 40:349, 1967
41. Makino S, Ouellette JJ, Reed CE, Fishel C: Correlation between increased bronchial response to acetylcholine and diminished metabolic and eosinopenic responses to epinephrine in asthma. J Allergy 46:178, 1970
42. Parker CW, Smith JW: Alterations in cyclic adenosine monophosphate metabolism in human bronchial asthma. I. Leukocyte responsiveness to beta-adrenergic agents. J Clin Invest 52:48, 1973
43. Kind LS: The altered reactivity of mice after inoculation with *Bordetella pertussis* vaccine. Bacteriol Rev 22:173, 1958
44. Ouellette JJ, Reed CE: Increased responses of asthmatic subjects to methacholine after influenza vaccine. J Allergy 36:558, 1965
45. Busse WW: Decreased granulocyte response to isoproterenol in asthma during upper respiratory infections. Am Rev Respir Dis 115:783, 1977
46. Bush RK, Busse WW, Flaherty D, Warshauer D, Dick EC, Reed CE: Effects of experimental rhinovirus 16 infection on airways and leukocyte function in normal subjects. J Allergy Clin Immunol 61:80, 1978
47. Buckner CK, Clayton DE, Ain-Shoka AA, Busse WW, Dick EC, Shult P: Parainfluenza 3 infection blocks the ability of a beta-adrenergic receptor agonist to inhibit antigen-induced contraction of guinea pig isolated airway smooth muscle. J Clin Invest 67:376, 1981
48. Busse WW, Anderson CL, Cooper W: Cortisol protection of the granulocyte response to isoproterenol during an *in vitro* influenza virus incubation. J Allergy Clin Immunol 67:178, 1981
49. Ida S, Hooks JJ, Siraganian RP, Notkins AL: Enhancement of IgE-mediated histamine release from human basophils by viruses: Role of interferon. J Exp Med 145:892, 1977
50. Welliver RC, Kaul TN, Ogra PL: The appearance of cell bound IgE in respiratory tract epithelium after respiratory syncytial virus infection. N Engl J Med 303:1198, 1980
51. Welliver RC, Wong RT, Sun M, Middleton E Jr, Vaughan RS, Ogra PL: The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. N Engl J Med 305:841, 1981