Respiratory infections precipitate wheezing in many patients with asthma. Although this association is most readily apparent in children, adults are also similarly affected. Considerable insight into this problem has followed detailed epidemiologic studies and from these observations have come important conclusions. First, viral, not bacterial, respiratory infections provoke asthma in children and adults. Second, although many respiratory viruses trigger asthma, the prevalent organism responsible for increased wheezing varies with the age of the affected patient. For example, respiratory syncytial virus (RSV) infections predominate in infants and young children, whereas rhinovirus, influenza, and parainfluenza emerge with greater frequency with increasing age. It is unlikely, however, that the mechanisms of virus-induced wheezing are different for each virus. Rather, a common mode of asthma exacerbation should be the rule. Third, the likelihood of increased wheezing with colds is greater when patients have severe symptoms such as malaise, fever, coryza, etc. Finally, there is new evidence that sinusitis, presumably bacterial in origin, may be a special situation in the relationship between respiratory infections and asthma. Our attention, however, will be directed toward the effects of viral respiratory infections.

Respiratory viral infections are not only important precipitants of asthma, but evidence also argues that they assume a significant role in the pathogenesis of airway hyperresponsiveness and asthma. The basis for this hypothesis is perhaps best illustrated by the consequences of RSV bronchiolitis in young children where a significant number of youngsters experience recurrent episodes of wheezing. Moreover, many adult patients date the onset of asthma to a severe respiratory infection. Therefore, not only do viral respiratory infections provoke attacks of asthma, but they may also be a pivotal component in the pathogenesis of bronchial hyperreactivity. Progress is ongoing to understand more completely how respiratory viral infections enhance airway reactivity and provoke asthma. In particular, new evidence indicates an intriguing relationship between respiratory infections, the development and promotion of immediate hypersensitivity responses, and the pathogenesis of airway hyperreactivity.

The Relationship of Respiratory Infections to the Development of Virus-Specific IgE Antibody

The allergic patient has IgE-specific antibody attached to mast cell membranes. Interaction of antigen with its specific IgE antibody bridges membrane-bound immunoglobulin and activates the cell's secretory process. With allergen-triggered asthma, the pulmonary mast cell becomes pivotal to the provocation of airway obstruction. It is now appreciated that release of mast cell products not only provokes acute bronchospasm, but also contributes to the development of delayed asthma or the late phase reaction (LPR). Airway obstruction following LPR tends to be more chronic, associated with heightened airway reactivity and pathologically characterized by bronchial inflammation. Recent efforts to understand the mechanisms of virus-induced asthma have focused on the relationship and influence that respiratory viral infections have on IgE-dependent immediate hypersensitivity reactions.

Welliver and colleagues were first to show convincingly that respiratory viruses can act as antigens and stimulate virus-specific IgE antibody production. In an initial study, exfoliated respiratory epithelium from infants and younger children with respiratory syncytial virus (RSV) illnesses was analyzed for cell-bound IgE. During the acute phase of illness, nearly 75 percent of all patients had IgE on respiratory tract cells. When the patients were stratified into patterns of clinical illness (upper respiratory tract illness, pneumonia, bronchiolitis or asthma) an interesting relationship
emerged. Three weeks after the onset of RSV respiratory illness, nearly 100 percent of patients with asthma or bronchiolitis had IgE bound to epithelial cells. In contrast, only 25 percent of patients with upper respiratory disease or pneumonia alone demonstrated a similar pattern. This increased frequency of cell-bound IgE was maintained in patients with bronchiolitis or asthma throughout the study. Interestingly, patients with a greater frequency of IgE on respiratory cells also had a higher incidence of previous episodes of wheezing or a family history of asthma. Thus, the increased frequency of cell-bound IgE in children with RSV illnesses correlated with the presence of obstructive airway disease.

In subsequent work, Welliver et al. extended their observations by quantitating the titer of IgE-specific RSV antibody in children with bronchiolitis. Nasal secretions were collected during acute and convalescent phases of illness and the titer of RSV-specific IgE antibody measured. From these data, the investigators discovered an interesting correlation between titers of RSV-IgE antibody and the pattern of respiratory illness. Children with either pneumonia with wheezing or bronchiolitis had higher titers of virus-specific IgE antibody at both acute and convalescent periods when compared to youngsters with upper respiratory illness or pneumonia without wheeze. Two other relevant observations were made: (1) the degree of arterial hypoxia correlated to the level of RSV-specific IgE titers (the higher the IgE titer, the greater the degree of hypoxia), and (2) the concentration of histamine in nasal secretions was greater in those individuals with pneumonia with wheezing or bronchiolitis.

Welliver et al. also examined the same question in children with parainfluenza respiratory illnesses. The pattern of IgE antibody response to parainfluenza virus was similar to observations in patients with RSV infections: parainfluenza virus infections in some children were associated with production of virus-specific IgE, IgE titers were higher in patients with croup and/or wheezing, and nasal secretions contained greater amounts of histamine when airway obstruction accompanied their clinical illness.

Although a strong association exists between levels of virus-specific IgE antibody titers in patients and a propensity towards airway obstruction during RSV episodes of bronchiolitis and parainfluenza respiratory infections, it is premature to conclude that virus-specific IgE antibodies directly cause or participate in the pathogenesis of airway obstruction. Nonetheless, it is difficult not to envision a scenario in which virus-specific IgE antibody becomes mast-cell bound, interacts with a respiratory virus-antigen to release vasoactive and inflammatory compounds, and thus causes bronchial obstruction. Confirmation of this hypothesis must await further study, but findings showing elevated levels of airway histamine and a correlation between histamine with hypoxia and the concentration of IgE antibodies, strongly implies that such a possibility occurs.

To further evaluate the significance of virus-specific IgE, Welliver et al. monitored 38 infants, prospectively, for 48 months after an initial episode of bronchiolitis. Only 20 percent of infants with undetectable titers of RSV-IgE titers had subsequent episodes of documented wheezing. In contrast, 70 percent of infants with high RSV-IgE antibody titers experienced wheezing on later occasions. To explain this observation, the authors questioned whether infection by RSV produces long-term abnormalities in airway function to make some children susceptible to recurrent wheezing or whether RSV infection in early age identifies individuals with airways congenitally prone to obstruction. The investigators conclude that their results, which suggest that the number of wheezing episodes experienced following RSV bronchiolitis can be predicted on the basis of a genetically determined phenomenon (over production of IgE), are more consistent with the concept that the increased frequency of lower respiratory tract illnesses, airway hyperreactivity, and small airway dysfunction observed in children examined years after an episode of bronchiolitis are also genetically determined.

However, many questions remain unanswered. Specifically, does the virus-specific IgE antibody have functional properties that allow it to attach to pulmonary mast cells, interact with virus (RSV or other virus), cause mediator release, and finally that this series of events leads to airway obstruction? Although unknowns exist today, present evidence convincingly shows that some respiratory viruses stimulate specific IgE antibody production. Precisely how this virus-specific antibody contributes to virus-induced asthma and asthma pathogenesis awaits further investigation.

The Effects of Virus Infections on IgE Immunoregulation

When Frick and co-investigators investigated infants born into families highly predisposed towards allergic diseases (both parents had allergies), an intriguing temporal association between viral respiratory tract infections and the onset of allergy, as measured by IgE specific tests and clinical symptoms, was noted. Although proof for this relationship is not directly available from these studies, it does suggest a "facilitative" role for certain viral infections in IgE immunoregulation in the allergy-prone individual.

To further evaluate this relationship, dogs were given pollen extracts and IgE antibody measurements made in animals given either live attenuated distemper-hepatitis virus vaccination or nothing. The
vaccinated puppies produced more IgE antibody to pollen than unvaccinated littermates. Moreover, when pups were given an intranasal canine parainfluenza virus vaccine followed by pollen inhalation and littermates only the pollen exposure, more IgE antibody to pollen was produced in the parainfluenza vaccinated dogs than the unvaccinated littermates. Frick and colleagues conclude that in atopic prone children and inbred dogs, viral infections can alter immunoregulation of IgE and thereby influence the development of allergic disease. Although the site of dysfunction in IgE immunomodulation is not identified in these studies, the authors suggest that the "allergy-prone" individual may be more susceptible to a loss of T-regulatory cell balance. Consequently, the virus infection temporarily alters T-cell regulation and a subsequent "breakthrough" in the production of IgE occurs at a critical time.

Further insights into the influence of viral respiratory infections on allergic sensitization come from observations by Sakamoto et al. Influenza virus-infected and control mice were exposed to antigen by aerosol and subsequent IgE sensitization quantitated. IgE titers to ovalbumin were greater in the influenza virus-infected animals than the control mice. Histologic examination of lungs from influenza-infected mice showed acute inflammation, peribronchiolar infiltration with mononuclear cells, and exfoliation of bronchial epithelia. Based on this information, Sakamoto et al hypothesized that airway inflammation increases epithelial permeability for antigen and the likelihood of IgE sensitization. Since many viral respiratory infections damage human airway epithelium, the relevance of this mechanism for IgE sensitization is also of obvious importance.

A number of conclusions follow from these observations. First, respiratory viral infections can stimulate the production of virus-specific IgE antibodies. Interestingly, patients with higher IgE titers to virus are more likely to have bronchitis or wheezing. Why certain subjects are more prone to develop IgE antibodies and what the role of virus-specific allergic antibody is in airway disease has yet to be established. Second, evidence suggests IgE sensitization to antigen, other than the virus, can follow damage to bronchial epithelia because antigen permeability is increased. Finally, a temporal relationship exists between appearance of IgE antibodies and a recent virus infection in allergy-prone children. The precise relationship and contribution of IgE-virus-specific antibody to the pathogenesis of current airway disease is, however, not clear. Nonetheless, the conclusion that virus-specific IgE antibodies are relevant in the pathogenesis of asthma is strengthened by the prospective analyses that recurrent episodes of wheezing are more frequent in patients with high IgE titers.

The Effect of Respiratory Viruses on Leukocyte Histamine Release

The consequence of an allergic reaction, and its corresponding tissue response, will be dictated by three general parameters: IgE sensitization of mediator releasing cells (mast cells and basophils), bridging of membrane-bound IgE molecules to release bronchospastic and inflammatory mediators, and finally, and perhaps most important, the response of the target organ which, in asthma, is the bronchial smooth muscle. Evidence has already been presented that respiratory viruses fulfill one component of this equation— IgE production. The influence of viral infections on mediator release is also of potential importance to the cause or promotion of airway smooth muscle contraction and inflammation.

Human leukocytes were used as an in vitro model to assess the effect of respiratory viruses on mediator release. When suspensions of isolated human leukocytes (containing mononuclear cells and basophils) were incubated in vitro with respiratory viruses, IgE-dependent histamine release was enhanced. Enhancement in mediator release also occurred with inactivated virus and paralleled the in vitro production of interferon. Furthermore, if leukocytes were incubated with interferon, rather than respiratory virus, histamine release was greater. Thus, enhanced basophil secretion of histamine follows exposure to respiratory viruses, or products of virus-infected cells such as interferon. The significance of basophil histamine secretion, or its enhanced release process, to the pathogenesis of asthma has yet to be ascertained as basophil involvement in asthma is not established. However, if a similar enhancement in mast cell mediator secretion occurs during respiratory infections, more profound airway obstruction would be the consequence. Data to address this latter issue are not presently available.

Human Models for Virus-Induced Airway Reactivity: Altered Autonomic Nervous System Function

To better understand the role of viral respiratory infections in the pathogenesis of airway hyperresponsiveness, it is essential that selected and well controlled studies be conducted in human subjects. In this regard, it is fortunate that changes in airways function and responsiveness occur in the non-asthma patient during viral respiratory illnesses. Although alterations in pulmonary physiology in the non-asthmatic with a cold are subtle and transient, they are predictable and consistent. For example, when normal individuals are ill with a viral respiratory infection, pulmonary obstruction develops but is primarily limited to small airway function. Such changes in small airway function are not clinically compromising but a consis-
tent, reproducible finding. Furthermore, alterations in respiratory physiology, although subtle, exist for weeks after clinical resolution of the viral illness. Thus, study of the consequences of a viral respiratory illness in nonasthmatic subjects can provide insight and clues to similar events in the asthma patient.

**Viral Respiratory Infections Enhance Airway Cholinergic Sensitivity**

Notable increases in airway reactivity accompany viral respiratory infection in some normal individuals. Increased airway reactivity in the non-asthmatic subject is usually not clinically apparent, but, like changes in small airway function, persists for weeks beyond the viral illness. We propose that when similar changes occur in the patient with asthma, who has pre-existing airway hyperresponsiveness, alterations in both obstruction and reactivity are exaggerated, clinically apparent and likely to persist for weeks beyond the bronchial infection.

Empey and colleagues\(^1\) documented significantly increased airway reactivity to aerosol histamine in 16 non-asthma patients with a viral upper respiratory infection. The cold-associated increase in airway resistance to aerosolized histamine was reversed by an inhalation of isoproterenol to indicate the change in responsiveness was related to bronchoconstriction. Furthermore, enhanced airway reactivity to histamine was prevented if the cold-subjects were premedicated with an aerosol of atropine. Increased airway reactivity (as indicated by a greater cough response to citric acid) was also blocked by atropine. Based upon protective effects with atropine, the investigators\(^1\) concluded that increased airway reactivity relates to an exaggerated cholinergic reflex response. Cholinergic hyperresponsiveness was proposed to occur as a consequence of epithelial damage with exposure and sensitization of rapidly-adapting sensory vagus fibers. Exposure of the sensitized fibers to irritants or histamine led to enhanced reflex bronchoconstriction. Heightened airway reactivity persisted for weeks beyond the acute infection, the time necessary for bronchial epithelial repair to occur.

**Viral Respiratory Infections Diminish Beta-adrenergic Function**

Airway smooth muscle contains beta-adrenergic receptors which are activated by circulating or administered catecholamines to maintain normal bronchial tone or to cause bronchodilation. Nearly two decades ago, Szentivanyi\(^2\) proposed that an imbalance in autonomic nervous system control contributes to overriding bronchoconstriction in asthma. A further impairment of beta-adrenergic function during viral respiratory illnesses would accentuate the existing airway hyperresponsiveness and potentiate bronchial constriction. Although it has not been possible to show evidence which convincingly identifies the basis of diminished beta-adrenergic function in asthma, many investigators find defective beta agonist activity in asthma. Earlier studies from our laboratory used isolated human leukocytes from asthma patients as an in vitro model to evaluate beta-adrenergic function in asthma.\(^3\) Incubation of isolated polymorphonuclear leukocytes (PMN) with isoproterenol stimulates cellular cyclic AMP production to reduce release of lysosomal enzymes. This PMN response provided a model for beta-adrenergic in human asthma.

Diminished PMN beta-adrenergic function exists in subjects with active asthma who had not been taking adrenergic medication for at least two weeks.\(^13\) This indicates that PMNs from asthma patients have impaired beta-adrenergic function which is not caused by anti-asthma medications. PMN beta-adrenergic function was further evaluated during a clinical viral respiratory infection which provoked asthma. PMNs from these patients had reduced responses to isoproterenol and a concomitant increase in asthma (a fall in their FEV\(_1\)). Furthermore, if isolated PMNs were incubated with either live rhinovirus or influenza virus, a similar reduction in beta-adrenergic activity developed.\(^14,15\) Our observations show that a viral respiratory infection, which provokes asthma, or an in vitro incubation with respiratory virus diminishes beta-adrenergic activity of human PMNs. The mechanism by which viruses alter PMN beta-adrenergic response has not been determined. However, it has been reported recently that structural similarities exist between the receptor for reovirus type 3 and the beta agonist.\(^16\) Whether this similarity in structure implies that viruses combine with beta receptors to change their function is not known nor is it known whether other viruses have similar properties.

Comprehensive studies to identify defects in human airway smooth muscle beta-adrenergic activity, either in asthma or as a consequence of a viral respiratory infection, have not been undertaken. Nonetheless, the significance of defects in leukocyte beta-adrenergic function may be important in and of themselves. Catecholamine activation of beta-adrenergic receptors on human leukocytes diminishes chemotaxis, lysosomal enzyme secretion, generation of superoxide, and histamine release. Changes in beta-adrenergic function would diminish catecholamine modulation of leukocyte function and potentiate neutrophil-driven inflammation. Since leukocytes exist in asthmatic airways and can be activated there, diminished beta-adrenergic function would increase leukocyte-dependent inflammation to thus accentuate bronchial reactivity and obstruction. Therefore, even though airway smooth muscle beta-adrenergic function may not be affected by respiratory viruses, promotion of bronchial reactivity...
obstruction could be a consequence of altered leukocyte function.

**Role of Rhinovirus Upper Respiratory Infections in Bronchial Hyperreactivity**

Two recent publications by Halperin and associates\(^7,8\) question the importance of rhinovirus upper respiratory infections in the development of lower airway reactivity and provocation of asthma. The first study evaluated 19 healthy volunteers experimentally infected with rhinovirus. Spirometry, measurement of airway reactivity by histamine bronchial provocation, and bronchoscopy were performed and compared to baseline values. No significant change in spirometry or airway reactivity to histamine occurred when rhinovirus infected and non-infected subjects were compared. However, cultures from bronchoscopy grew rhinovirus from infected subjects. Because it is impossible to eliminate the possibility that viruses were introduced into the lower airway by bronchoscopy, the significance of this observation remains difficult to ascertain. Nonetheless, the possibility exists that rhinovirus grows in lower airways during upper respiratory infections.

Halperin et al\(^9\) conducted similar analyses in patients with asthma. Nineteen of 21 patients inoculated with rhinovirus became infected. No significant change in pulmonary function was noted in the patients when evaluated as a group. However, four asthma patients had greater than a 10 percent fall in FEV\(_1\). In contrast to the other rhinovirus-infected asthma patients, these four also had increased airway reactivity to histamine. Although the authors conclude that their data suggest "that the importance of viral infection as a cause of wheezing episodes in adult asthmatics should be reevaluated," their observed frequency of increased asthma in adults during a viral upper respiratory infection is not different from previous reports by Minor et al\(^10\) or Hudgel and co-workers.\(^10\) Thus, rhinovirus infections may provoke wheezing in some, but not all asthma patients, and the parameters which determine the outcome of this response cannot be ascertained from past studies or those of Halperin et al.\(^8\)

Clinical impressions and published reports of prospective studies of children\(^21\) strongly argue that rhinovirus is an important respiratory infection in the precipitation of asthma. We are equally convinced that many factors, including characteristics of the infecting viruses, dictate the outcome of respiratory illnesses on airway function. To address these issues, we have begun studies in which patients are experimentally infected with rhinovirus and the consequence of respiratory illness can be examined in a prospective manner. Preliminary results have provided us with both insight into mechanisms of virus-induced asthma and direction for future study.

In a just completed project, ten patients with allergic rhinitis were infected with rhinovirus 16 (RV16). The RV16 was selected for inoculation because it was the rhinovirus type previously isolated from patients during acute clinical episodes of asthma.\(^22\) For a number of reasons, we chose to evaluate the effects of a rhinovirus illness first in allergic rhinitis subjects rather than asthma patients. Although patients with allergic rhinitis do not have clinical asthma, their airway responsiveness is often enhanced when compared to normal subjects. Secondly, patients with allergic rhinitis do not have underlying abnormal airway smooth muscle characteristics of asthma (hyper trophy, hyperactivity, or inflammation) to complicate the effects of respiratory illness on pulmonary function. Thirdly, none of the patients required bronchodilator medication which could also interfere with the interpretation of changes in airway function. Finally, we were concerned that an acute respiratory infection may provoke an attack of wheezing in patients with underlying asthma.

To qualify for entry into our study, all subjects had the absence of circulating antibody to the infecting virus (RV16), positive immediate hypersensitivity skin test response to ragweed (an antigen used for basophil histamine release and antigen bronchoprovocation) and released histamine when leukocytes were incubated in vitro with ragweed antigen. In conducting these studies, patients were seen on three different occasions, each separated by one month. Baseline (pre-infection) studies included quantitation of bronchial reactivity to inhaled histamine and ragweed antigen by determining the PD\(_{20}\) values (provocative dose to drop the FEV\(_1\), 20 percent). In addition, leukocyte histamine release to ragweed antigen was measured. Following establishment of baseline values, patients were seen one month later and inoculated with RV16. Confirmation of infection was made by recovery of virus from nasal washes and/or a four-fold rise in virus-specific antibody at convalescence.

All ten patients had evidence of a rhinovirus infection following inoculation. During the acute infection, all patients had a significant increase in airway responsiveness to histamine and antigen. The relative enhancement in airway reactivity during the rhinovirus infection to histamine and antigen was similar. Thus, our data suggest that rhinovirus infection significantly enhances airway reactivity to histamine and antigen.

We also evaluated the patients for development of a late phase asthma (defined as a greater than 15 percent drop in FEV\(_1\) approximately six hours post-antigen challenge). At baseline (pre-infection studies), only one of ten subjects had a late-phase reaction (LPR) to antigen. However, during acute rhinovirus infection, eight of ten subjects experienced LPR. From our
analyses, the likelihood of late-phase asthma to antigen was not predicted by the degree of underlying airway reactivity or the difference in airway reactivity from baseline to acute viral illness, but rather appeared to be independent of changes in airway reactivity. This suggests to us that events involved in the development of LPR to antigen are particularly susceptible to enhancement during rhinovirus infection. Moreover, since LPR is more similar to chronic asthma than acute bronchospasm, the rhinovirus effects on LPR may hold important clues to the pathogenesis of virus-induced airway reactivity and possibly the very pathogenesis of bronchial hyperresponsiveness in asthma.

In addition, the effect of rhinovirus infection on basophil histamine release was evaluated. During acute rhinovirus infection, leukocyte histamine release to ragweed antigen was significantly enhanced over baseline values. At present, the significance of the basophil to asthma and changes in airway reactivity during the viral URI is not apparent, but two observations suggest a possible explanation for them in asthma. We previously found basophil release of histamine ("releasability") correlated with the degree of airway reactivity in asthma. That is, the greater the amount of leukocyte histamine release following activation, the greater the degree of bronchial reactivity. Further, investigators at Johns Hopkins have characterized mediator secretion from nasal tissue following antigen challenge; their observations suggest that the late phase response in the nose (symptoms and mediator release) involves basophil participation. Based on these observations, we speculate that: (1) a change in basophil release represents, or parallels, a general alteration in mediator secretion which may also exist with mast cells, (2) the enhanced basophil secretion may be an important factor in the development of late phase reaction, and/or (3) the change in basophil releasability may be important to enhanced airway reactivity. Such conclusions are presently speculative but of considerable interest to us for future study.

The Effect of Respiratory Infections on Airway Responsiveness

Although studies with humans are invaluable to gain further insight into the mechanisms of virus-induced bronchial hyperresponsiveness, they have certain limitations. In particular, functional assessment of respiratory virus effects on isolated airway smooth muscle cannot be made; thus, we have developed an animal model for virus-induced asthma. Parainfluenza 3 (P-3) infected guinea pigs have many characteristics similar to effects of respiratory infections in human subjects. In P-3 infected animals, in vivo airway reactivity to histamine is enhanced and in part mediated by an exaggerated vagus reflex. Study of isolated smooth muscle, in contrast, shows normal contractile responses to acetylcholine and histamine. Interestingly, however, isolated airway smooth muscle from P-3 infected animals has enhanced contraction to neupeptide substance P. To further define the mechanism of virus effects on airway response to substance-P, inhibitors of the lipooxygenase pathways of arachidonic acid metabolism were tested. In tissue from non-infected animals, the contractile response to substance P was increased in the presence of lipooxygenase inhibitors. In contrast, inhibitors of lipooxygenase pathway did not change bronchial contraction to substance P in tissues from infected guinea pigs. These observations suggest that P-3 infection blocks release of a bronchodilator product of the lipooxygenase pathway from epithelial cells or the action of such a product is absent after virus infection. As a consequence of this virus effect, airway smooth muscle contraction to substance-P is potentiated. Since histologic examination of P-3 guinea pig airways reveals inflammation and epithelial damage, such a possibility is not only intriguing but possible.

Summary

From this review, it is apparent that the effects of respiratory viral infection on airway reactivity are multiple. Although virus-associated changes are many, we have at present no evidence to show that respiratory viruses cause intrinsic abnormalities in airway smooth muscle function. Rather, respiratory viruses influence bronchial smooth muscle function through a variety of other means: epithelial injury, PMN-dependent inflammation, and greater mediator release. These observations suggest that a common pathway to development of airway hyperreactivity during respiratory viral illnesses is to enhance those factors which participate in the inflammatory response. When the target of this enhanced inflammatory response becomes the airway, greater bronchial reactivity and obstruction result. Although many questions remain to be answered, we feel that future studies to evaluate the biology of respiratory virus effects on mechanisms of airway responsiveness will lead to a greater understanding of asthma pathogenesis.

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