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10

Stress, Viral Respiratory Infections, and Asthma

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i. Introduction

Asthma is one of the most prevalent of chronic diseases worldwide. It is a chronic inflammatory disorder of the airways associated with intermittent and reversible airway obstruction. Current thinking about the pathogenesis of asthma is that inflammatory processes in the airways result in a limitation of airflow and an increased responsiveness of the airways that causes them to narrow in reaction to certain stimuli (1). Allergens and respiratory infections are the primary contributors to airway inflammation. Allergens are also common triggers of airway constriction, but so are air pollution, cold air, exercise, odors, and certain respiratory infections. Clinical wisdom has long suggested that psychological stress and related emotional factors may also play an important part in promoting airway inflammation, airway constriction, and triggering symptoms (2). Indeed, asthma patients and the physicians who treat them often report that stress and emotional factors can initiate, trigger, or exacerbate asthma symptoms. Data to corroborate this assumption, however, are relatively scarce, and the clinical significance of psychological factors in asthma remains unclear (3).

The theory that asthma has a psychosomatic component has existed at least since the early 1920s, when classic psychoanalytic studies generated the hypothe-

sis that asthma represented in part the psychosomatic manifestation of intense emotion (4,5). At the same time, learning theorists argued that particular emotional experiences may have reinforced pulmonary physiological responses, thus increasing the likelihood of their recurring in the same context (6). The connection between asthma and emotion was based on the observation that emotionally laden stimuli could elicit small but reliable changes in the airways of asthmatic individuals (7). Conversely, the observation that asthmatic individuals experienced improvement in their respiration following relaxation procedures provided further clinical evidence supporting the idea that emotions played an important role in asthma (reviewed in Ref. 7).

Contemporary studies of the role of stress in asthma are consistent with this view. Both adult and child asthmatics report and display more negative emotion than others (reviewed in Refs. 8, 9), and asthma exacerbations have been linked temporally to periods of heightened negative emotionality (9–11). The causal interpretation of these data is, however, muddied by the possibility that asthma was the cause of the emotional distress rather than the distress causing asthma. Experimental studies of the effects of emotional stimulation on pulmonary function and other relevant physiology of asthmatics have provided a clearer interpretation of the direction of causation. When subjected to stressful experiences such as performing mental arithmetic tasks (12), watching emotionally charged films (13,14), or listening to stressful interactions (15), 15–30% of asthmatics respond with increased bronchoconstriction (reviewed in Ref. 16). The susceptibility to stress-induced constriction is not attributable to age, gender, asthma severity, atopy, or method of pulmonary assessment (16).

This chapter examines the behavioral, neural, and immune pathways that might link psychological stress to the onset or exacerbation of asthma. This focus emphasizes the role of central nervous system (CNS) interaction with immunological and endocrinological processes in explaining the association between psychological stress and airway changes in asthma (17). It also focuses on stress-elicited increases in susceptibility to and severity of respiratory infections as a major link between psychological stress and asthma.

II. What Is Stress?

When confronting environmental demands, people evaluate whether the demands pose a threat and whether sufficient adaptive capacities are available to cope with them (18). Threat evaluation is based on the personal values of the individual as well as the magnitude of the threat. Evaluations of coping abilities depend on past experience, personality, and the availability of material and social resources. If environmental demands are found to be taxing or threatening, and at the same time coping resources are viewed to be inadequate, we perceive ourselves as being under stress. This perception is presumed to result in negative emotional states including fear, anger, anxiety, and depression. The perception of threat

and the concomitant emotional state trigger brain-based physiological responses, which in turn result in changes in autonomic and immunological activities. Hormones and neuropeptides released into the circulation when people experience stress are thought to play roles in regulating both inflammatory and airway responses (19).

Psychological stressors have been associated with the activation of the autonomic nervous system and of the hypothalamic-pituitary-adrenocortical (HPA) axis. Both the sympathetic and parasympathetic components of the autonomic system are responsive to psychological stress. The sympathetic system reacts with increased output of epinephrine and norepinephrine from the adrenal medulla and norepinephrine from adrenergic nerve endings (20). Increased sympathetic activity is generally accompanied by withdrawal of vagal tone. Certain types of stimuli, however (e.g., those requiring heightened vigilance or outward deployment of attentional resources), cause parasympathetic nervous system activation. Individuals differ widely in the magnitude of their autonomic reactions to behavioral stimuli—both sympathetic, parasympathetic, and balance of the two.

The hormonal responses of the HPA axis have long been thought to represent a nonspecific physiological reaction to excessive stimulation (21), particularly the emotional arousal associated with appraising situations as stressful (18,22). The hypothalamus releases corticotrophic-releasing hormone (CRH), which triggers the anterior pituitary gland to secrete adrenocorticotrophic hormone (ACTH), which in turn activates the adrenal cortex to secrete corticosteroids (primarily cortisol in humans). More recent work suggests that negative emotional responses disturb the regulation of the HPA system. For example, relatively pronounced HPA activation is common in depression, with episodes of cortisol secretion being more frequent and of longer duration among depressed than among other psychiatric patients and normals (23). Shifts in the circadian rhythm of cortisol have also been found among persons in stressful situations (24).

Although hormones of the autonomic nervous system and HPA are those most often discussed as the biochemical substances involved in stress responses, alterations in a range of other hormones, neurotransmitters, and neuropeptides have also been found in response to stress and may play an important role in stress influences on asthma. Examples include stressor-associated elevations in growth hormone and prolactin secreted by the pituitary gland and in the natural opiate beta-endorphin and enkephalin released in the brain (25). These substances are also thought to play a role in immune regulation (26).

Psychological stress and its biological concomitants can last for a few minutes or for years. Chronicity is to some degree based on the ongoing presence of external stimuli that triggered the stress response (e.g., ongoing unemployment) but is also dependent on the long-term success of individual coping resources. Moreover, events that last a very short time can have very long-term stress effects. Such effects are thought to be maintained by recurrent "intrusive"

thoughts about events (27). Elevations of circulating catecholamines and cortisol also seem to be maintained by recurrent intrusive thoughts but are thought to habituate in response to many chronic stressors. Moreover, even if the circulating levels of these hormones remain elevated, there is often a downregulation of receptors over time, resulting in a habituation of the hormone effects.

III. How Could Stress Affect Asthma?

Figure 1 provides a simplified picture of the pathways that might link psychological stress to asthma. Psychological stress may influence asthma through autonomic, immune, or behavioral pathways. However, the strongest suggestion from the current literature is that stress may influence the pathophysiology of asthma by increasing the risk of respiratory infections, which play important roles as both promoters of airway inflammation and triggers of asthma. We will present existing evidence suggesting the plausibility of each of these mechanisms.

Asthma, of course, can also trigger psychological stress. For example, severe shortness of breath can result in a panic response based on the patient's perception that their symptoms are a threat and are beyond their control. Such an appraisal would trigger the same behavior and biological responses discussed above and further contribute to the disease event and feelings of helplessness associated with it. Asthma medications can also increase physiological activation

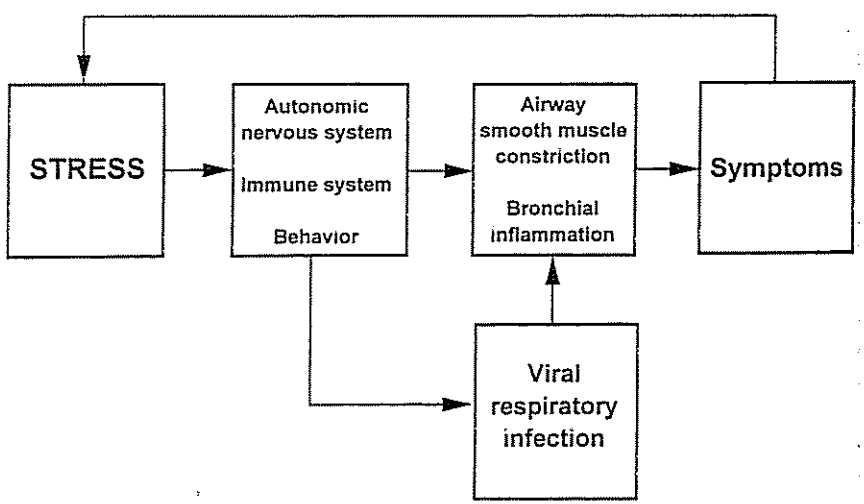

Figure 1 Pathways hypothesized to link psychological stress to asthma.

and concomitant emotional response, triggering the same pathways as external stressful events (9).

A. Behavior Pathways

There are a range of behavioral responses to stress that can contribute to asthma. These include panic-type responses to acute stressful events such as crying, yelling, and hyperventilation that can trigger airway constriction by drying or irritating airway walls. Stress may also elicit deep breathing that can lead to reflex bronchoconstriction in asthmatics. Other behavioral responses include acute and chronic stress–elicited disruptions of adherence to behavioral strategies that help prevent or limit asthma events. Strategies that may be affected by stressful events include the avoidance of indoor and outdoor allergens, air pollutants, and the use of certain drugs. They also include adherence to monitoring symptoms and lung function and proper adherence to medication regimens. Stress is also associated with smokers reporting need for a cigarette, smoking more cigarettes, and being less successful at quitting or cutting down on smoking (28,29). Smoking triggers and exacerbates asthma symptoms by irritating the airways, increasing mucus production, increasing susceptibility to respiratory infections, and altering immune function (30).

B. Autonomic Pathways

The argument that psychological stress might influence autonomic control of the airways is based primarily on the fact that many of the same autonomic mechanisms thought to play a role in asthma are involved in the activation and regulation of physiological responses to stress. These include the release of sympathetic nervous system hormones, the action of adrenergic (sympathetic) and cholinergic (parasympathetic) nerves, and the neurotransmitters and neuropeptides they produce.

The parasympathetic nervous system innervates the airways via efferent fibers that travel in the vagus nerve and synapse in small ganglia situated in the airway wall, from which short postsynaptic fibers directly supply the airway smooth muscle and submucosal glands (31). Previously, increased activity of the parasympathetic nervous system was thought to be the dominant mechanism responsible for the exaggerated reflex bronchoconstriction seen in asthmatic patients (32). More recent work, however, has shown that although parasympathetic mechanisms are involved, they are not a major cause of airflow limitation in asthma (33). In the initial phases of asthma, narrowing of the airways is thought to be attributable primarily to inflammation. However, bronchial constriction is due to some combination of vagal afference plus inflammatory product stimulation, with the relative importance of these factors depending on genetic and environmental influences.

Recent experimental studies in which asthmatic patients are exposed to stressful situations have focused on stress-induced vagal reactivity as a mediator of emotionally induced bronchoconstriction (9). This includes preliminary evidence that children with asthma who respond to stressful stimuli with high vagal activation (associated with increased cholinergic activity) have greater impairment of airway reactivity in response to methacholine (14).

Although human airway smooth muscle is not functionally innervated by adrenergic axons (34,35), studies have demonstrated adrenergic innervation of submucosal glands, bronchial blood vessels, and airway ganglia (36). Adrenergic agonists bind to adrenoceptors on the surface membrane of effector cells in the airways resulting in a variety of airway changes. Depending on the type of agonist (beta or alpha) involved, these changes can variably affect airway smooth muscle, release of inflammatory mediators, cholinergic neurotransmission, mucus secretion, and possibly mucociliary clearance, resulting in either bronchodilation or bronchoconstriction. Adrenoceptors are regulated by norepinephrine, which is released locally from sympathetic nerves and by epinephrine and norepinephrine secreted by the adrenal medulla. The regulatory effects of epinephrine and norepinephrine on adrenoceptors suggest a plausible mechanism by which stress-induced activation of the sympathetic nervous system might influence bronchomotor tone.

A glaring paradox for the argument that activation of the sympathetic nervous system by stress might contribute to bronchoconstriction is that beta agonists act to relax airway muscle and are used to treat active symptoms. Consequently, acute psychological stress, which is accompanied by a quick elevation in circulating catecholamines, might be expected to result in bronchodilation. However, after the stressor is terminated, epinephrine and norepinephrine levels quickly return to normal or below normal levels.

There are individual differences in the relative strength of sympathetic versus parasympathetic control in response to certain forms of stress, with some individuals showing a predominantly parasympathetic response (vagal tone). Such individuals might be particularly susceptible to stress-induced bronchoconstriction (9). Moreover, as noted earlier, certain types of stimuli activate a predominantly parasympathetic response. It is also possible that sympathetic activation itself might contribute to asthma symptoms. For example, elevations of circulating epinephrine and norepinephrine are known to alter a number of immune parameters that might contribute to inflammation of the airways. Prolonged elevations of these hormone levels under chronic stress might also contribute to asthma severity. For example, chronic daily use of beta agonists in mild to moderate asthmatics with a specific genetic predisposition may increase severity by downregulating beta receptors (37). It is possible that chronically elevated catecholamines could do the same for genetically susceptible subgroups.

Recent evidence suggests functional interactions between peptides released by neurons and the classic neurotransmitters that allow complex integration and regulation of functions in the airway (33). Clearly, the potential role of psychological stress and its physiological concomitants in such interactions is not understood. However, the fact that stress has been associated with modulation of many of the hormones, neurotransmitters, and neuropeptides involved in autonomic control of the airways suggests that further investigation is warranted.

C. Immune Pathways

A focus on the inflammation of the airways in asthma has drawn attention to the possibility that stress-induced alterations in immune response might have implications for development, exacerbation, and triggering of asthma (3,8). There is now a substantial human literature demonstrating that psychological stress can influence cell trafficking, cell function including mitogen-stimulated blastogenesis and natural killer cell cytotoxicity, as well as lymphocyte production of cytokines (38). Stress can modulate immune response through nerve pathways connecting the autonomic nervous and immune systems, by triggering the release of hormones and neuropeptides that interact with immune cells, and through side effects of behaviors such as smoking and drinking alcohol that are adopted as ways of coping with stress (26,39).

Humans exposed to cognitive or social laboratory stressor tasks lasting only a few minutes show suppression of T-cell mitogenesis and increased numbers of circulating T-suppressor/cytotoxic (CD8) cells and natural killer cells (40). These effects are thought to be mediated by the autonomic nervous system because they occur quite rapidly (41), have been shown to be associated with increases in heart rate, blood pressure, and circulating catecholamines (41,42), and are blocked by administration of an adrenoceptor antagonist (43). Studies of naturalistic stressors show similar alterations of immune response (see review in Ref. 39). Living near the Three Mile Island nuclear power plant at the time of the accident, care-taking for a relative with Alzheimer's disease, and taking medical school exams have all been shown to influence both numbers and functions of various populations of lymphocytes. This includes stress-elicited alteration of the production of the cytokines IL-1β, IL-2, and IFN-γ (e.g., Refs. 44,45).

Stress is not expected to have the same effects on immune function in all people. As noted earlier, individual differences in response to stressful events are attributable to interpretation of the event and access to coping resources. However, there is also evidence of stable individual differences in immune response that occur independent of psychological response to the stressor. When exposed to multiple acute laboratory stressors over time, some subjects consistently demonstrate stress-elicited alterations in immunity, while others do not (46,47). Interestingly, these differences are not associated with their emotional response to the stressors (47).

The contemporary view of asthma pathogenesis is that a chronic inflammatory process involving the airway wall causes the development of airflow limitation and increased responsiveness that predisposes the airway to constrict in response to certain stimuli (1). Mechanisms of airway inflammation involve a cascade of events that include the release of immunological mediators triggered by both IgE-dependent and IgE-independent mechanisms (1). In more than 80% of cases, asthma is an allergic disorder and is orchestrated by antigen-triggered interactions of T and B lymphocytes, and includes B-lymphocyte synthesis of IgE induced by T-helper (TH) cell release of interleukin (IL)-4. The IgE antibody attaches to and activates basophils, mast cells, eosinophils, and platelets, resulting in the release of mediators that are thought to orchestrate the inflammatory cascade. In addition to involving IgE, appropriate antigen can trigger T lymphocytes to release cytokines, which attract and activate leukocytes, particularly eosinophils to the airway walls, and thus directly provoke the inflammatory cascade (1).

Currently, there is no evidence that the stress-altered characteristics of human immunity we have discussed contribute directly to asthma pathogenesis. However, asthmatic high school and college students respond to final examinations with the changes in cytolytic and proliferative responses characterized earlier as immune responses to stress as well as alterations that might influence the physiology of asthma including increased release of inflammatory superoxides by neutrophils (48).

It seems paradoxical that psychological stress activates the HPA resulting ultimately in the release of cortisol, which has anti-inflammatory effects. However, recent evidence suggests that CRH, which regulates the HPA response, has proinflammatory effects in the periphery. This includes triggering mast cell degranulation and increased vascular permeability (49). Moreover, acute psychological stress (by immobilization in rats) resulted in skin mast cell degranulation, and this effect was inhibited by anti-CRH serum administered prior to stress (49).

The discussion of the inflammatory response in asthma has recently emphasized the role of activated T-helper (TH) cells and the cytokines they produce, particularly IL-4 and IL-5. These cytokines are thought to initiate and orchestrate the complex cellular events in airway inflammation and hyperresponsiveness (50,51). Studies of allergic asthmatic subjects with active disease or challenged with antigen show that eosinophil recruitment to the airway is a major factor in inflammation and that IL-4 and IL-5 are instrumental in this process.

TH cells have two phenotypes: TH-1 and TH-2. TH-1 cells produce IL-2 and interferon (IFN)-γ but little IL-4 or IL-5 and provide B-cell help for the production of protective antibodies, predominantly IgG (52). In contrast, TH-2 cells produce IL-4, IL-5, IL-6, and IL-10 but little IFN-γ and provide B-cell help primarily for the production of IgE in response to allergens. The development of asthma may be associated with a predominance of TH-2 cytokine production (53).

Both environmental and genetic factors are thought to determine which TH cell phenotype becomes more prevalent after the first months of life (53). For example, Martinez et al. (54) provided evidence suggesting that certain lower respiratory tract infections in early life (primarily croup) enhance the production of IFN-γ by nonspecifically stimulated lymphocytes, believed to be an expression of TH-1 type behavior. However, it is possible that stress-triggered hormones in the early months of life influence TH-2 cell predominance. This could occur through a direct influence of stress hormones on the production of cytokines thought to modulate the direction of differentiation. Although there is no direct evidence for stress influencing TH phenotype differentiation in the developing immune system, there is evidence that parental reports of life stress are associated with subsequent onset of wheezing in children between birth and one year (55).

Psychological stress in adults may also alter TH-1 and TH-2 cytokine production. The administration of examinations to medical students was associated with an increase in lymphocyte production of IL-2 (45) and a decrease in the production of IFN-γ (44). A similar study of high school students, however, failed to find that exams produced differences in production of TH-1 and TH-2 cytokines (56).

Overall, there is substantial evidence for both acute and chronic stress influencing a broad range of cellular and humoral immune responses, including influences on the number of and function of cells involved in the inflammatory response. Recent work also suggests that stress might influence the production of cytokines produced by T-helper cells that are the constituents of the TH-1 versus TH-2 predominance thought to play an important role in the development and course of asthma. Hopefully, future research will clarify the potential role of stress in airway inflammation in asthma.

D. Respiratory Infections as a Pathway

The strongest suggestion from the current literature is that psychological stress may influence the pathophysiology of asthma by increasing the risk of respiratory infections. This is based on evidence of the role of respiratory infections as both promoters of airway inflammation and triggers of asthma, for stress-induced suppression of immunity (discussed earlier), and for stress-induced risk for the development of upper respiratory infections.

As discussed earlier, some infections during childhood are thought to alter the development of the immune system in a manner that reduces the chances of subsequent allergen sensitization (53). In contrast, it has been suggested that severe infections with RSV may enhance allergy sensitization and the risk of developing asthma (57). This literature suggests that the effects of infection may depend on which pathogen infects the host early in immune development (58).

Respiratory viruses exacerbate disease among both children and adults with asthma (58). Respiratory infections can both promote airway inflammation and

act as a trigger for asthma expression. Viral respiratory infections provoke wheezing in many asthma patients. Respiratory syncytial virus, parainfluenza virus, rhinovirus, and influenza virus are the most frequently identified viruses associated with increased wheezing (59–61). Rhinovirus in particular has been implicated in the majority of the exacerbations of asthma in children (62). The role of viral respiratory infections as triggers for asthma exacerbations also appears to be important in adults (63).

A number of mechanisms may be involved in explaining the exacerbation of asthma, especially wheezing and increased airway responsiveness, by viral respiratory infections. First, viral respiratory infections may cause damage to the airway epithelium causing airway inflammation. Another mechanism involves the stimulation of virus-specific IgE antibody. Respiratory syncytial virus and parainfluenza virus may potentiate the allergic response to allergens by increasing the release of inflammatory mediators from mast cells and the subsequent cascade of inflammatory events characteristic of asthma (64,65). Lastly, viral respiratory infections may also result in the appearance of a late asthmatic response to inhaled antigen (66). Thus, there is evidence that viral infections are an "adjuvant" to the inflammatory response and promote the development of airway injury by enhancing airway inflammation (67).

As discussed earlier, psychological stress has been shown to have a broad impact on the regulation of the human immune system. One potential consequence of stress-induced changes in immune response is suppression of host resistance to infectious agents, particularly agents that cause upper respiratory disease. The primary evidence for such effects comes from studies investigating psychological stress as a risk factor for the common cold, influenza, and other respiratory infectious diseases. Prospective epidemiological studies have demonstrated that both children and adults reporting chronic family stress have a greater subsequent incidence of serologically verified upper respiratory infections and more symptom days of respiratory illness (68–70). Similar results are reported in studies predicting the incidence of influenza during flu season (71).

Increased incidence of upper respiratory infections under stress in the epidemiological studies may be attributable to stress-induced increases in exposure to infectious agents, rather than stress-induced changes in host resistance. Control for exposure is provided by studies in which volunteers are intentionally exposed to a virus (viral-challenge trials). In these prospective studies, psychological stress is assessed before volunteers are exposed to an upper respiratory virus and monitored in quarantine for infection and illness. Using this paradigm, psychological stress has been associated with the incidence of infection and illness with increasing stress related in a dose-response manner to increasing risk (72–74). These relations were found across seven different common cold viruses including rhinoviruses types 2, 9, 14, 39, and Hanks, respiratory syncytial virus, and coronavirus 229E. Moreover, risk of infectious illness has been found to increase with increased duration of the stressful experience (73). Studies of disease severity have similarly found that psychological stress measured prior to viral exposure was associated with more severe colds and influenza as measured by both symptom reporting and by the amount of mucus produced over the course of the illness (75). These associations cannot be explained by differences in health practices among low- and high-stressed persons, and it is speculated that they are attributable to differential production of inflammatory cytokines in response to infection. Elevated levels of both epinephrine and norepinephrine in 24-hour urines are also associated with increased susceptibility in the rhinovirus trials (76).

In sum, psychological stress is associated with decreased host resistance to a wide range of respiratory infectious agents. Included are rhinoviruses and respiratory syncytial virus, both of which contribute to asthma pathophysiology. Although there is currently no direct evidence for stress influencing asthma through susceptibility to respiratory infections, existing evidence lends considerable credence to this hypothesis.

IV. Conclusions

Both patients and clinicians have long believed that psychological stress plays an important role in the pathogenesis of asthma. Although some evidence for such a relation has accumulated over the years, there is little direct evidence of how a psychological response is translated into effects on physiological pathways that influence the course of asthma. This chapter has presented a range of pathways through which psychological stress might influence asthma pathophysiology. These include stress-elicited changes in patient behavior, in autonomic response, in immune response, and in host resistance to respiratory infections. Although all of these systems are influenced by stress, there is only scattered evidence demonstrating ties between stress, the proposed pathways, and asthma pathogenesis. Hopefully, future research will focus on directly testing the types of models proposed here and hence provide a clearer understanding of the association between stress and the onset and progression of asthma.

We view the existing evidence for stress-induced susceptibility to respiratory infections as the most promising of the proposed mechanisms. This is because of the simplicity of this model, the evidence that stress operates as a risk factor for both incidence and severity of upper respiratory infections, and evidence that respiratory infections operate as risk factors for both the onset of asthma and for the triggering of symptoms in asthmatics. This view is strengthened by growing evidence of the role of stress in modulating the inflammatory response of the immune system.

The most challenging characteristic of our current knowledge is that some but not all asthmatics respond to stress with an exacerbation of disease. It is similarly believed that only a subset of those at risk for asthma are subject to stress-induced onset (3). Susceptibility to stress may be attributable to specific

kinds of asthma or specific kinds of psychological characteristics. Relevant typologies of asthma subtypes might be based on the mechanisms that play the predominant role in disease expression (8) or on lability of hyperactivity of the patient's airways (77). Psychological subtyping might be based on dispositional psychological or physiological responsivity to stressful events (14,46,47). Alternatively, it might be based on individual differences in the appraisal of threat posed by specific types of events. It is also possible that there is genetic susceptibility to stress-induced asthma onset or stress-induced exacerbation (3,8).

We have presented the emotional response to psychological stress as if it were a unitary undifferentiated response. This is an oversimplification. Different types of stressful events are thought to induce different responses, as are differences in individual interpretations of events. Intense emotional expressions that have been traditionally associated with triggering or exacerbating asthma include anger, anxiety, excitement, fear, and frustration (10,11,16). It is important to determine which emotional responses influence asthma, whether these are just airway responses or include inflammatory responses, and what the mechanisms are that link emotional response to asthma.

Finally, there is increasing evidence that interventions designed to reduce stress have palliative effects of asthma symptoms. Less clear is which patients are amenable to intervention and why and whether specific types of intervention are as effective as others.

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11

General Virology and Targets for Therapy

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I. Introduction

There have been many important advances in our understanding of the role played by viruses in the clinical problems of asthma and related diseases. The purpose of this essay is to look again at some general features of the biology and behavior of viruses in order to see how they fit into what we know of the condition and to look for guidance as to where significant new advances might be made.

A huge number of viruses are now known to science, and their structure and behavior are amazingly diverse, although we shall ignore the viruses of insects, plants, and bacteria and consider only those of warm-blooded vertebrates (Table 1). Fortunately, although we need to think of some of the viruses that affect farm animals, those involved in asthma all belong to the group commonly called respiratory viruses of humans. To molecular biologists this is an unsatisfactory classification, for it brings together viruses with profound differences in their genome. Some encode genes in DNA, but many more use RNA, and in many the particle contains a positive sense strand while in some it is negative stranded; profound differences in the strategy of virus replication result from this. Proteins, some of which are enzymes, are encoded by the genes and synthesized with the ribosomes of the host cell. In some cases they condense around nucleic acid and