Psychologic Stress and Asthma: Neuropeptide Involvement

In a recent Grand Rounds in Environmental Medicine article, Wright and Steinbach (*1*) highlighted the influence of psychosocial stress on asthmatic attacks. The reported case histories support basic neuroimmunologic studies, which document modulation of immune reactivities by psychologic stress, and the need to consider psychologic stress along with environmental chemical and physical stresses, which alone or in combination can alter physiologic homeostasis resulting in ill health (*2,3*). With the four case histories described by Wright and Steinbach (*1*), the influence of emotional factors is brought into context with physiologic disturbances, and the reference to violence as "an unrecognized environmental exposure" emphasizes the need to make more researchers aware of the impact that psychologic status can have on neuroimmune interactions and health (*4*). Wright and Steinbach (*1*) stated that their report was "... to alert clinicians and researchers to a potential risk factor [psychologic stress] for increased asthma morbidity that has not previously been recognized." However, it has been known for more than a century that cognitive neural circuits can alter immune responsiveness. In 1886, a New England physician demonstrated that individuals with an allergy to roses could have an allergic response triggered by the perceived presence of the allergen, an artificial rose (*5*). Thus, allergic responses can be elicited in the absence of allergen, and asthma has been reported to occur with emotional changes (*6*). Although it may be argued that not all asthmatic episodes are allergic or even immunologically driven, there is substantial evidence connecting immune responses and asthma, and it is well documented that the nervous system can regulate immune functions. More specifically, it has been suggested that neural control of airways is involved in the pathogenesis of asthma (*7*), but the mechanistic connections have not been confirmed (*8,9*). As referenced by Wright and Steinbach (*1*), central nervous system involvement in asthma is related to environmental stresses that can occur from psychologic disturbances. Although, to date, the involvement of specific neurotransmitters or neuropeptides has not been fully delineated in asthmatic processes, neuropeptides from C-fibers of the sensory (sympathetic) nervous system, which innervate the lungs as well as other organs (*10*), are known to have multiple effects on immune reactivities.

Vasoactive intestinal peptide increases mast cell trafficking (*11*); nerve growth factor (NGF) and substance P influence mast cell development and degranulation (*12–14*); and histamine from mast cells is known to induce asthmatic responses. Another cell associated with asthma is the eosinophil; calcitonin gene-related peptide, substance P, and vasoactive intestinal peptide enhance eosinophil chemotaxis (*15,16*). Neuropeptides also can modulate IgE synthesis, which is implicated in allergic asthma (*17*). Interestingly, in a report by Larsen et al. (*18*), a mouse strain that produced an IgE response to aerosolized ovalbumin (BALB/c mice) had an enhanced airway response to electrical field stimulation, but a strain that produced mainly IgG did not show an enhanced response. The enhanced BALB/c response could be transferred to a nonimmunized syngeneic mouse by peribronchial lymph node cells; the authors suggested that the lymph node cells from sensitized BALB/c mice altered neural control of airways (*18*). Further complexities of neuroendocrine immune circuit involvement in airway physiology/pathology, as well as other immune-associated pathologies, have been documented with production of regulatory neuropeptides by lymphocytes and macrophages (*19–23*) and immune cytokine alteration of neuropeptide production (*24,25*). A posited link between allergies and depression also has been suggested (*26*). In addition, psychologic influences on lymphocyte proliferation (*27*) and multiple other immune parameters (*4*), including lung infection (*28*), have been reported.

More to the point of the psychologic impact on asthma, neuropeptides, which can be immunomodulatory, are released by emotional stress. The influence of psychologic stress on asthma was the topic of a workshop sponsored by the National Institutes of Health (NIH) (*29*). Research regarding neural control of airways has been recommended by the NIH and the World Health Organization to be an area that requires further research (*30*). Exercise (*31*) and hyperventilation from physical or emotional stresses (*32*) can initiate an asthmatic attack. Analyses of childhood asthma have shown substantial interfacing between the biology of asthma, behavior, stress, and immune reactivities (*33*). Psychologic stress increases NGF production as well as receptors for NGF on lymphocytes (*34,35*). NGF release is especially problematic for asthmatic patients because, in addition to its effects on mast cells, NGF is known to cause negative regulation of glucocorticoid receptors (*36*), and inhaled glucocorticoid is a major therapy for asthma. The various cell types, neuropeptides, and immune factors involved in asthma are pieces to the puzzle, but these interconnecting pieces need to be mechanistically associated before the mysterious rise in asthma incidence can be further understood.

The types of interorgan regulatory controls (e.g., between the endocrine, immune, and nervous systems exemplified by the reported violence and asthma associations) indicate the need for multidisciplinary approaches to disease analyses. It is often necessary to take a reductionistic approach in order to focus on the mechanisms of a single cell type. The complextities of any one system demand substantial attention. However, no one organ system functions independently of other organ systems. Just as psychologic, chemical, and physical stresses can team to alter health, teams of researchers with different experiences will be needed to unravel the multidirectional pathways controlling responses to environmental factors. Psychoneuroimmunology research has been ongoing for almost a quarter of a century, and most mechanisms remain elusive. Toxicant effects on the neuroendocrine immune circuitry (neuroimmunotoxicology research) is even less far along (*37*), but researchers need to consider the psychologic stress on their animals when evaluating the mechanisms associated with their favorite toxicant. Lack of appreciation for psychologic effects may increase the variances within results, which could especially be important for therapeutic drug trials.

The potential involvement of psychologic stress (one form being violence) on asthma has not actually been unrecognized; it is a research area that has been neglected.

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Psychologic Stress and Asthma: Wright's Response

The overall aim of our recent Grand Rounds in Environmental Medicine article (*1*) was to alert clinicians and researchers to exposure to violence specifically (not stress) as a largely unrecognized risk factor contributing to asthma morbidity. This is certainly true in the arena of clinical medicine. Moreover, research on the health effects of violence has typically centered on direct exposure of individuals to violent acts (*2–4*). More recently, investigators have focused on large population studies to explore the effect on health outcomes of living in a violent environment, with a chronic pervasive atmosphere of fear and the perceived threat of violence (*5–7*). A growing body of research has explored potential adverse psychologic consequences on children growing up in chronically violent neighborhoods and homes (*8,9*). Notably missing, however, are population-based studies that examine possible adverse implications that growing up in a violent environment may have on physical health, and specifically on chronic disease expression.

In our paper (*1*), we also discussed multiple plausible pathways through which living in a violent environment may influence asthma expression, including stress; health behaviors and psychologic factors; access to health care; and potentiation of an individual's response to other environmental exposures (e.g., viruses, allergens). We concur with Lawrence that increased understanding of the complex cellular and molecular basis of airway obstruction and airway inflammation (*10*)—in parallel with evidence of important interactions among behavioral, neural, endocrine, and immune processes—provides fresh insight into means by which psychosocial stress may influence the development and expression of asthma (*11*). The evidence cited by Lawrence only serves to further support our argument that experienced stress may be one mechanism through which exposure to violence is operating. It is also important to consider how violence in communities might contribute to the paradox of deficient asthma care among people who live almost literally in the shadows of leading urban medical centers. Community-based barriers such as high violence or crime rates may result in more limited access to pharmacies for needed prescriptions or in the diversion of funding away from asthma care facilities (*1*). Our paper (*1*) emphasizes the complex nature of possible interrelationships between violence and asthma morbidity, drawing on significant insights from many disciplines (i.e., sociology, psychology, epidemiology, trauma, geography, psychoneuroimmunology). Given the complex nature of the interrelationships between violence (at both the individual and societal level) and asthma, we strongly concur with Lawrence that any attempt to unravel associations must take a multidisciplinary approach.

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The *a Posteriori* Probability of a Kidney Cancer Cluster Attributed to Trichloroethylene Exposure

In a letter commenting on the analysis of trichloroethylene (TCE) epidemiology by Wartenberg et al. (*1*), Borak et al. (*2*) called into question the statistical interpretation of the key study by Henschler et al. (*3*) on the grounds that the Henschler study, although cast and analyzed as a cohort study, was based on a previously recognized cluster of kidney cancer cases. In reply, Wartenberg and Reyner (*4*) stated that

> the results of Henschler et al. … were so extreme (5 cases where 0.628 were expected) that the probability of observing such a situation is less than 5×10^{-5}, under Poisson assumptions. In other words, if there were no association, one would have to search for 500,000 similar workplaces with comparable TCE exposures to find such occurrence due to chance alone.

In fact, a closer examination of the issue shows that the result of Henschler et al. (*3*) is not at all unexpected as a result of chance alone when it is encountered as a cluster that calls attention to itself after the fact. Wartenberg and Reyner's (*4*) approach to this question is appropriate in principle—comparing the cluster result against an articulated statistical null hypothesis—but it is mistaken in execution. In the first place, 5×10^{-5} corresponds to 1 in 20,000, not 1 in 500,000. Second, for an expected number of 0.628, the correct Poisson probability of observing an outcome as extreme as 5 cases is actually about 4.8×10^{-4}, an order of magnitude less unusual than Wartenberg and Reyner state. Third, the calculation of the number of workplaces needed for one among them to have a randomly generated apparent cluster does not acknowledge that this is a matter of probability.

The probability 4.8×10^{-4} represents the chance of finding 5 or more cases in a single particular place where circumstances lead to an expected number of cases of only 0.628. The probability that such an extreme outcome would happen by chance at least once among a large number, *N,* of such places, all subject to the same chance events, is given by $1 - (1 - 5 \times 10^{-4})^N$; that is, it is 1 minus the probability of observing no instances of extreme outcomes in the collected set of *N* places.

The probability that, by chance alone, an apparently "extreme" outcome occurs in at least one unspecified location goes up surprisingly rapidly with the number of locations that are considered. In this particular case, by chance alone there is a 5% probability that at least 1 of 106 locations would show an outcome judged to have an *a priori* probability < 4.8×10^{-4}. The odds are even (50% probability) that one would find at least 1 instance of such an "extreme" outcome among 1,431 places, and it takes only 6,184 places subject to the random effect to be virtually assured (95% probability) that at least 1 of them will show an outcome as extreme as that observed by Henschler et al. (*3*) in terms of calculated *a priori* probability. These numbers are far less than the 500,000 workplaces that Wartenberg and Reyner (*4*) cite as being necessary.

In practice, when evaluating an apparent cluster, it is difficult to be precise about the number, *N,* of places that comprise the universe of locations in which a cluster could potentially be observed under the null hypothesis of randomness. In interpreting the study of Henschler et al. (*3*), one should not confine consideration to workplaces with trichloroethylene exposure because such exposure is part of the after-the-fact association with the particular outcome in the particular factory where (under the null hypothesis of randomness) the unusual co-occurrence of five cases happened to be observed, and such a random occurrence could have happened in a quite different kind of workplace. The appropriate *N* would seem to include all workplaces in Germany (or in Europe, or in the world) in which an apparent cluster of kidney cancer cases could in principle have been recognized. Given that only just over 1,000 such places need exist before one expects to encounter a random occurrence of clustering of kidney cancer cases as extreme as seen by Henschler et al. (*3*), the observation of the particular cluster is not at all unexpected by chance alone.

The magnitude of difference between *a priori* and *a posteriori* probabilities is counterintuitive because we tend to forget about the "denominator"—the many places subject to the same random occurrences where an unusual confluence of cases did not occur and call attention to itself—but the difference is demonstrable by calculation. When considered properly, the weakness of arguments based on clusters recognized after the fact, and the dangers of faulty reasoning regarding them, are apparent. It is for these reasons that epidemiologic studies need to be designed and interpreted in terms of *a priori* risks.

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Canadian Hot Weather Health-Response Plan

In a recent issue of *EHP,* Smoyer-Tomic and Rainham (*1*) reported increased mortality among those older than 64 years of age in Toronto, Ontario, Canada, when the humidex ranged between 30 and 35°C. In all probability, the rising humidex temperatures would concurrently affect potency and bioavailibility of therapeutics offered to patients in clinical practice.

Therapeutic agents require constant storage in a controlled temperature range—from a sub-zero temperature to either 2–8°C or 25–30°C. Inadvertent exposures to high humidity and temperature would alter the potency of the medicines. That was evident during a field exercise in Nigeria when the active ingredients in 48% of the common therapeutics were outside the limits specified by the British Pharmacopoeia (*2*). An identical scenario could not be ruled out in Toronto or elsewhere. During the mid-1990s in Toronto, vaccines were properly refrigerated only in 47.5% of general and pediatric practices. Furthermore, only 10% of these practices kept a record of refrigerator temperature, and in 33% of sites, the temperature range was outside the recommended range (*3*). A well-controlled temperature and humidity in warehouses with stocks of pharmaceuticals cannot guarantee full potency of medicines, and the temperature and humidity in households are not necessarily appropriate for all medications and do not remain constant.

Prospective hot weather health-response strategies will not be comprehensive unless they address any cryptic loss in potency and bioavailability of the therapeutic agents used in households. Failures should be assessed in the field. Simple assay formats that could accomplish qualitative and quantitative analysis of therapeutics in the clinical and household setting should be standardized. Recently, Green et al. (*4*) proposed a quick and simple test that requires few chemicals and no sophisticated equipment to identify artesunate, an antimalarial drug, in the field. Identical tests for frequently used medicines would confirm the quality of medicines consumed when humidex values exceed 30–35°C in Toronto or anywhere in the world. Also, such a strategy would address

the quality of medicines irrespective of any warm-climate health susceptibility dependent on age above 64 years (*1*).

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Hot Weather and Therapeutic Agents: Response to Arya

Our evaluation of hot weather health-response strategies was geared toward estimating and preventing excess deaths from heat stress (*1*). The issues regarding storage of therapeutic agents that Arya raises are important ones, however. To expand on his point, the effects of ambient weather conditions should be broadened to include health impacts associated with physiologic heat sensitivity stemming from medication use, medication-induced photosensitivity, and pharmacokinetics, as well as storage (*2*). Although there is little evidence that ambient heat and humidity affect absorption and elimination of orally administered drugs, there is evidence of pharmocokinetic interactions for transdermally and subcutaneously administered drugs, such as insulin and nitroglycerin (*3*). Because medication use is most prevalent in older populations, who are also at greatest risk of heat stress, Arya's points about including therapeutics in hot weather health warnings are important, particularly for the elderly.

Heat indexes, like humidex (used in Canada) and apparent temperature (used in the United States) are more appropriate than temperature alone for human health effects. Although they can be useful in predicting high-risk periods for medication-induced weather and ultraviolet radiation sensitivity and for pharmocokinetic changes, heat indexes are not readily applicable to nonliving organisms. Thus we do not recommend them for advisories about proper storage of therapeutic agents. Most agents are effective only within a range of temperature and humidity values, which should be evaluated separately rather than as a composite heat index when considering proper storage conditions. Nonetheless, hot weather health-response information could address the issues raised here and by Arya through wide dissemination to health providers and pharmaceutical suppliers and users.

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