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Emergent Asthma

Endogenous, Exogenous, or Iatrogenous

In search for the possible causes of the emerging and persistent increase in the prevalence of asthma, Eneli et al in this issue of *CHEST* (see page 604) consider the evidence that the occasional, frequent, or prolonged intake of the analgesic acetaminophen (N-acetyl-*p*-aminophenol [APAP], or paracetamol) might be a contributing etiologic factor. As the authors speculate, APAP could account for pulmonary glutathione depletion, oxidative stress, T-helper type 2 (Th-2) vs T-helper type 1 dominance, leukotriene C_4 and D_4 formation, or cyclooxygenase-2–induced prostaglandin E_2, which favors a Th-2 response and thus an allergic tendency. But whatever the case might be, it must be recognized that this "reversible" or variable obstructive intrabronchial disease[1] is a clinical manifestation of diverse etiology, course, and prognosis. To study all "asthmatics" as a single set, either for basic research or for epidemiologic surveys, would be incorrect and potentially misleading. The results of any long-term risk assessment will have to be interpreted in the perspective of the spectrum of specific circumstances and of known or suspected influences.[2]

Almost 40 years ago, in 1966, when the husband-and-wife team of the Ishizakas in Denver identified the reaginic antibody Ig E (IgE) [the "E" chosen to refer to the wheal and erythema skin reaction] as the major endogenous component of allergy, headlines in some popular news media announced a "breakthrough in asthma."[3] But, contrary to a projected "optimistic future,"[4,5] allergic diseases and the various kinds of asthma have persistently become more widespread and, not infrequently, more severe,[6,7] requiring continuous daily medication that may include antiinflammatory steroids, the use of which in earlier decades had been called "malpractice."[8] This significant epidemiologic phenomenon of emergent asthma has evoked the notion of "a new disease," which 4 centuries ago was applied to the novel appearance of rickets.[6] If iatrogenous (not iatrogenic, which literally means causing, not caused by, medical intervention) processes are found to be responsible for that, an analogy would seem appropriate with the fate of the mythical Greek king Oedipus, who pledged to relieve his city of the plague, not aware that the cause of it was himself, due to the "pollution" of his patricide and incest.[3] Whether or not the main features of the modern "plague" relate to medical and health-care practices, a realistic appraisal of the available data ought to guide further self-examination and critical assessment.

The classification of asthma into extrinsic and intrinsic, first proposed by Rackemann,[9] has endured. Additionally, distinctions between mild, moderate, and severe have helped formulate appropriate therapeutic guidelines.[10] Naturally, age, sex, occupation, home environment, and variability patterns, etc. have helped to distinguish subgroups. One diagnostic category, the atopic syndrome, is a phenotypic response to external natural or man-made environmental and dietary antigens among individuals with an inheritable capacity to produce specific IgE antibodies. The correlation of an elevated asthma risk with the early onset of atopic eczema, in the first 6 months of life,[11,12] questions the role of microbial immunity and/or drug-induced alterations in the airways, events that generally are subsequent to the first manifestations of dermatitis.

Elevated IgE, characteristic of atopic sensitization, at 1 year of age, has been reported to be a predictive index for asthma by the age of 2 years.[12] In that study,[12] the risk could be significantly reduced by medical advice for environmental control and breast feeding. Prenatal influences, including maternal use of APAP,[13] have been associated with an increased incidence of allergy in the child. More precisely, antenatal cytokine production, detected with changes in cord blood interleukins (ILs), among them IL-6, IL-10, interferon-γ, and other mediators, appeared to herald the development of allergic disease by the age of 6 years.[14] In general, infections have been repeatedly considered—not only by clinicians but also by the patients' families—as the most important triggers of paroxysmal asthma. Until not very long ago, empirical formulations of bacterial vaccines were—and still seem to be in certain limited practices—part of the maintenance immunotherapy injection program for asthma. Current data[15] incriminating specific infectious agents in acute attacks or an exacerbation of persistent asthma indicate the need for further controlled studies.

The well-known protective effect of breast feeding against allergic disease appears to be antithetical to the observed reduction of risk after exposure to food-borne and orofecal microbes.[16] Could maternal milk stimulate lymphoid tissue in the infant's digestive tract as microorganisms seem to do? And why does male gender double the risk of atopic allergy in early childhood,[11,17] or could it be that femininity—*ie*, the female gender—lowers it by 50%? The reports that the emergent asthma may be a result of modern hygiene are thought provoking. Markers of possible risk-reducing infections have been detected,[18] and appropriate therapeutic efforts are promising. The magnitude of the asthma "epidemic" has been shown in a longitudinal study in New Zealand,[19] which noted that at least one in four children reported wheezing, and that at age of 26 years, the end of the follow-up, 51.4% of the subjects had reported wheezing more than once (assuming that wheezing meant asthma).

The contrast between acute and chronic respiratory infections in lowering or raising the manifestation of asthma[15] might possibly relate to the degree of pyrexia with acute episodes. Fever, not only spontaneous but also experimental or therapeutically induced, has been shown to suppress asthma,[20,21] at times for extended periods or indefinitely. Alterations in hypothalamic-pituitary-adrenal function have been considered as an expression of beneficial febrile stress, what Selye[22] called *euponia*, a "good stress." Of course other, immunologic, mechanisms are still conceivable, especially in view of recently reported suppression of allergic airway disease—in mice—-with mycobacterial lipoglycans.[23]

Hormonal and neuropsychiatric abnormalities, along with endogenous and exogenous allergenic factors, must be recognized as significant contributing influences on both established and emergent asthma. The nearly complete remission—"outgrowing"—of asthma in adolescence[17] has been reexamined in the course of a iatrogenic or iatrogenous menopause and a second menarche[24,25] in a 36-year old woman, who, after having had severe steroid-dependent asthma since the age of 2 years, became symptom free without medication after a delayed (due to steroids?) puberty at age 16 years, when she also started taking an hormonal birth control preparation. Approximately 20 years later, chemotherapy had to be administered following mastectomy for a malignancy, and she stopped menstruating. Asthma then recurred and again subsided—not completely this time—when, approximately 6 months later, her hormonal cycle was resumed.

Drug-induced respiratory disease is actually subject to electronic monitoring, such as that found on www.pneumotox.com. The reported differences in the effects of selected nonsteroidal antiinflammatory drugs (NSAIDs) and APAP on asthma are hard to explain.[26] Aspirin-induced asthma has been noted with increasing frequency,[27] yet the review by Eneli et al indicates that, in contrast to APAP, aspirin may have a protective effect. Oral provocation challenges with aspirin have reproducibly resulted in acute anaphylactoid reactions among known or suspected hypersensitive persons, even with one tenth of ordinary therapeutic doses.[26] By contrast, in most challenges with APAP, amounts greater than the usual analgesic dose had to be administered to produce—not easily perceived subjectively—a drop of 15 to 20% in ventilatory capacity such as FEV_1. The recognized asthma-aspirin-nasal polyposis triad has been labeled *idiosyncratic*, due to the fact that no specific reaginic antibodies have been detected. The unexpected IgE antibody formation against APAP, quoted by Eneli et al will require confirmation or rebuttal.

Like other investigators who questioned the possibility that the original diagnosis, rather than any medication, might be the cause of the observed abnormalities, Eneli et al appropriately debate the problem of cause and effect regarding APAP and asthma. As in the case of hypertension,[28] the verdict tends to incriminate the analgesic. The increased incidence of adverse reactions to APAP among patients with more severe asthma may be indicative of the heightened susceptibility to idiosyncratic reactions to analgesics among patients with intrinsic asthma,[26] which is relatively more persistent and incapacitating. Possible cross-reactivity between NSAIDs and certain food dyes—*eg*, tartrazine—and preservatives has to be kept in mind[26] and so ought to be the potential harmful effects of herbal and similar "natural" medicaments.[8] Among the more ubiquitous environmental factors causing or aggravating asthma, mention must be made of air pollution[29] and climate.[30] An annual mean increase of 10% in indoor humidity was found to raise the prevalence of asthma in 12 countries by 2.7%. Violence (outdoors!) has been linked to an increase in asthma morbidity.[31] As with the multiple etiologic and precipitating stimuli outlined here, the "vulnerability" of subjects with asthma and the possible existence of some autonomic conditioning[32] can only be adequately assessed if this ventilatory disorder is considered not as a "straight-line" transition from health to disease, but as a cyclically amplified ("vicious circle") bronchoconstrictive oscillation.[33,34] In this respect, the possible destabi-

lizing effects of impulsive and injudicious medical intervention cannot be ignored.

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