



Guest Editorials

It's about time for allergenic extracts to undergo review

The allergy specialty depends on allergenic extracts for diagnosis and treatment of patients with allergic disorders. These essential tools-of-the-trade have served well for almost 100 years in various forms.¹ Initially, allergists produced their own extracts by obtaining raw materials, extracting them, and using them for diagnosis and treatment. During this home brew era, extract production did not fall under the jurisdiction of any regulatory authority. For many reasons, it was bad policy for allergists to make their own extracts, so extract production by commercial manufacturers was a significant advance.

Allergenic extracts are considered to be biologics, and hence they now fall under the jurisdiction of the Center for Biologics Evaluation & Research (CBER) of the Food and Drug Administration (FDA). There is a significant difference between a biologic and a drug. A biologic is defined by the process used for its production, and a drug is defined by its contents.² If one starts with a defined raw material and subjects it to a specific sequence of procedures, the final product could be an FDA-licensed biologic. Should any step in the manufacturing sequence be altered, a new biologic would be created, and a new license would likely be required before it could be sold. That is why biologics cannot easily be modified, leading to extracts that have remained essentially unchanged for decades despite new information about their components and manufacturing procedures.

Though the process of extract production can be standardized, its final biologic potency may vary from lot to lot and batch to batch. Extracts that do not meet defined potency requirements cannot be adjusted without modifying the production sequence, so they may have to be discarded. Methods for standardization have included comparison of new extracts with reference vials,³ the ID50EAL⁴ method for determining bioequivalent allergy units,⁵ and more recently the use of specific immunoassays for measuring individual components.⁶ This process took decades, resulting in a small number of standardized extracts, whereas most preparations remain unstandardized.

Now the allergy community faces a new challenge. Allergenic extracts have enjoyed a relatively protected status under the jurisdiction of CBER. Many extracts remain available even though there may be no evidence of their safety or efficacy. That situation is changing. The allergenic extracts branch of CBER has been evaluating the status of many extracts. During this interval, a window of opportunity remains to save some extracts that might otherwise be destined for the dust bin. The FDA has indicated that an extract may be salvaged if even the weakest of evidence exists for its safety and ideally for its efficacy. As allergists, we need to decide which of these extracts are worth saving. Through the herculean efforts of the authors of this perspective,⁷ allergenic extracts are now being

reviewed with a scrutiny that should have been applied years ago. And it is about time.

The perspective outlines the process that the FDA is using to review these extracts. Extracts are divided into 5 lists: those with sufficient evidence for diagnosis and treatment, foods, those with evidence for diagnosis, and those for which there is inadequate evidence for either. A fifth list includes extracts for which there are safety concerns.

A few at-risk extracts such as cockroach are unlikely to be removed because supporting evidence is available. Others probably should be deleted because they are listed by genus without a species, and more specific extracts are already protected. Many at-risk extracts, including many fungi, are probably effective but there is simply no evidence to support them. And some extracts are only relevant in a specific location, so there is a lack of interest in studying them. They should be kept but the evidence supporting this is unlikely to be forthcoming.

Once an extract loses its license, it is unlikely that it can ever be resurrected. Although any extract can undergo the type of rigorous diagnostic or therapeutic testing that other products undergo when seeking FDA approval, each extract would have to go through this process individually, potentially costing more than the total combined gross sales of the extract industry in a typical year. It would simply not be practical to subject each extract to such rigorous evaluation.

For now, our strategy should be to preserve extracts that are worth saving if evidence for efficacy exists. Having gone through this “spring cleaning,” the profession will be left with a smaller selection of reagents. But we should not stop there. Members of our profession should systematically evaluate each extract. This could be facilitated through a joint effort by the two national organizations, the American College of Allergy, Asthma & Immunology (ACAAI) and the American Academy of Allergy, Asthma & Immunology (AAAAI), perhaps with additional support from vendors, the National Institutes of Health (NIH), the FDA/CBER, and individuals. A registry of extracts should be created, standardized protocols developed, and forms written to facilitate approval by institutional review boards. Members of both societies could capture diagnostic accuracy rates, efficacy measures, and safety for each extract, using a type of crowd-sourced surveillance, as currently is done with immunotherapy reactions.⁸ The largest cross-section of allergists possible should be included in this effort rather than focusing on funding a small elite group of clinical investigators. Sophisticated statistical measures could be used to separate signals of individual extracts from mixtures. By using this approach, the current FDA review could result in improved extracts that would greatly improve our ability to diagnose and treat our patients.

Disclosures: Authors have nothing to disclose.

Jay M. Portnoy, MD
 Children's Mercy Hospitals & Clinics
 Kansas City, Missouri
 jportnoy@cmh.edu

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Ancient organisms and modern lifestyles

Human response to endotoxin has a long history in the immunology community. Nevertheless, the role of this biological polymer in the genesis and exacerbation of asthma remains unsettled. There are undoubtedly many discoveries related to endotoxin exposure and the human immune system yet to be made; a recent article by Sheehan and colleagues in *Annals*¹ make incremental but important contributions because it begins to place children's endotoxin exposure into the context of overall environmental exposure and asthmatic disease. Although we typically think of endotoxin exposure in agricultural and industrial environments, it is a substance that each one of us comes in contact with daily; at home, in daycare, in schoolrooms, and in the workplace.

Evolution of our understanding of endotoxin can be traced to *Limulus polyphemus*, an ancient organism that defended itself against the harmful effects of bacteria before mammals evolved. Its defensive mechanism centered on detecting the presence of endotoxin or lipopolysaccharide (LPS), substances common to many bacteria. Endotoxin entered the immunology sphere when animal experiments of the early 1960s indicated a single massive but sublethal dose given to young animals modified their endotoxin response as adults.² These experiments came to fruition with the awarding of a portion of a 2011 Nobel Prize to Bruce Beutler³ for demonstrating that toll-like receptor 4 is the LPS receptor. Endotoxin or its common constituent, LPS, are polymers on a similar theme but with varying components. Endotoxins are typically the size of small proteins (approximately 10 kDa) with polymeric aggregates sometimes approaching 100 times larger. Because they are identified more by their origin (bacteria) and recognition by *L. polyphemus* amoebocytes and human interleukin 14/toll-like receptor than for any structural homology, they are hard to quantify. Endotoxin is found nearly everywhere. Temperatures greater than 250°F for 30 minutes are required to destroy 99.9% of endotoxin even on clean glassware. An excellent history of the use of *Limulus* in the detection of LPS can be found on the Marine Biological Laboratory internet site.⁴

Paracelsus is credited with saying, "All things are poison, and nothing is without poison; only the dose permits something not to be poisonous." Endotoxin seems to fit this saying, because long-standing experiments with endotoxin have not fully determined whether it is a boon or a bane. Additionally, it is not merely the dose but also the route of exposure (intravenous or inhaled) that determines its significance. Important human-re-

lated effects of varying dose ranges and routes of exposure of endotoxin include: intravenous injection of nanogram amounts⁵ causes fever, and inhalation of large amounts produces asthma symptoms.

When inhaled by individuals with allergic asthma, endotoxin can exacerbate airway obstruction and inflammation⁶; and allergic individuals have heightened response to inhaled endotoxin.⁷ Experimental airway exposure to LPS in humans with asthma and mice modulates allergen response.⁸ However, mere exposure to endotoxin-containing dust does not produce airway disease. Factors including the genetic background of the exposed organism as well as the timing of the exposure appear to determine whether endotoxin has a positive or negative influence. Environmental endotoxin exposure does not occur alone but is accompanied by protein allergens, beta glucans, airborne fungi, and bacteria as well as communicable diseases, these days mostly of a viral origin.

With all of the contradictory information concerning endotoxin, and in light of the hygiene hypothesis, the reader likely wonders whether more endotoxin exposure might be better. Is exposure to an "endotoxin soup" good for the patient with asthma when viewed from a larger perspective? Endotoxin exposure is certainly higher in crowded environments such as Mumbai and Mexico City; however, these places have not been historically noted for high rates of asthma. The absence, in the present study, of a seasonal variation in endotoxin is interesting in light of the common belief that asthma attacks occur more frequently when school starts in the fall as outdoor aeroallergens peak and viral exposure increases. Perhaps inner-city children are better in school as opposed to being in their homes with multiple asthma triggers (smoke, allergens, cleaning agents, and so forth). Maybe the endotoxin helps them, or maybe it does not make any difference.

The study methodology is primarily designed to understand the sources and exposure of school endotoxin. The possibilities are that school endotoxin levels are derived from home endotoxin carried by the children, or there is some endogenous source of endotoxin production associated with the school itself. Perhaps crowding or the population density of the classrooms is a factor. The same factors are probably not operating in all schools, because 2 of the 12 schools have lower exposures, and 2 of the schools have essentially the same exposures as homes. Investigators did not offer any explanations why schools 10 and 11 had less endotoxin. The correlation between school cat and dog allergen levels and increasing dust endotoxin levels is interesting, because we presume cat and dog allergen is brought from

Disclosures: Authors have nothing to disclose.

Funding Sources: Financial support provided by Children's Mercy Hospital.