

Pathogenesis and management of anaphylaxis: Current status and future challenges

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This issue of the Journal is devoted to the subject of anaphylaxis. The assembled articles both reflect how much progress has been made in the basic understanding and clinical management of this disorder since it was given its current name about 100 years ago¹ and reveal how much work there is still left to do.

In introducing this topic to medical students, I usually start with a story of a child with severe peanut allergy. While at a friend's home, he was offered ice cream. Being well-schooled in how to avoid allergen exposure, he read the ingredients on the carton and saw that peanuts were not mentioned. However, on his first mouthful, he realized from the rapid onset of symptoms that peanuts must have been included. He was rushed to a local emergency room, but there apparently was a delay before he received epinephrine, and he died. It turned out that although peanuts in fact were not listed on the carton, they were included in the candy bar that was mentioned among the ice cream's ingredients.

This tragic tale and many others like it support the view that anaphylaxis, a catastrophic and sometimes fatal allergic reaction to what often is an otherwise innocuous substance, represents the most grotesque imbalance between the cost and benefit of an immune response. The events of this case also illustrate some of the significant challenges faced in dealing effectively with the patient education, public policy, and commercial and medical management issues that can affect efforts to prevent or, failing that, adequately treat individual episodes of this frightening disorder.

No one who has witnessed (or survived) an episode of anaphylaxis is likely soon to forget it, and recorded observations of this disorder extend far back into antiquity. It is thought that Pharaoh Menes died from an anaphylactic reaction to a wasp sting some 4500 years

ago.¹ Approximately a century ago, Charles R. Richet and Paul Jules Portier set out to develop an antitoxin to the venom of the Portuguese man-of-war (*Physalia physalis*). Instead, they discovered the reaction they termed *anaphylaxis*, taking *phylaxis* from the Greek for immunity or protection, and, according to one account, adding the *ana* in part to make the term euphonic.¹

Since that seminal work, our mechanistic understanding of this phenomenon has come a long way. There is now little reasonable doubt that the IgE-dependent activation of mast cells (and basophils) is the key event underlying most examples of antigen-induced anaphylaxis,² and many workers deserve credit for elucidating the important components of this pathogenetic pathway. As reviewed in this issue,³⁻⁵ although several individuals made important early contributions to efforts to characterize the elusive reagent of allergy, the discovery of the critical antibody isotype that contributes to many anaphylactic reactions in human beings, which ultimately was named *IgE*, was made independently by 2 pairs of investigators: Kimishige and Teruko Ishizaka, and S. G. O. (Gunnar) Johansson and Hans Bennich.

Henry Metzger and his colleagues identified the high-affinity receptor for IgE as a single molecular entity (FcεRI),⁶ and Jean-Pierre and Henry Kinet cloned and characterized the genes for the 3 components of this tetrameric receptor.^{6,7} Through the work of Henry, Jean-Pierre, and many others, it is now known that the aggregation of FcεRI that occurs in anaphylaxis and other clinical settings by the binding of FcεRI-bound IgE to bivalent or multivalent antigen induces the activation of mast cells and basophils, resulting in the rapid and, in the case of cytokines and chemokines, sustained release of diverse mediators, many of which can induce the pathophysiologic components of anaphylaxis.⁶⁻⁸ However, in both human beings and mice, clinical events that mimic many of the features of IgE-associated and mast cell-associated anaphylaxis, including the sometimes fatal outcome, can be induced by mechanisms that involve other pathogenetic pathways.² Moreover, in mouse models at least, such mechanisms can account for antigen-dependent anaphylaxis in the virtual absence of tissue mast cells or IgE.²

However, several lines of evidence now indicate that IgE can contribute to the intensity of anaphylaxis

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Received for publication December 21, 2004; accepted for publication December 29, 2004.

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J Allergy Clin Immunol 2005;115:571-4.

0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.12.1133

by mechanisms beyond simply sensitizing or priming mast cells and basophils to undergo activation and to release mediators when the cells encounter the antigen for which that IgE has specificity. IgE also has the ability, independently of its antigen specificity, to enhance significantly the effector function of these cells. The best understood mechanism by which this occurs is via IgE-dependent enhancement of the levels of surface expression of the FcεRI, which has been shown to increase IgE-dependent and/or antigen-dependent mast cell effector function, both in mouse models⁹ and in human beings in clinical settings *in vivo*.¹⁰

More recently, it has been reported that IgE, again in the absence of known specific antigen, can also enhance the survival of mouse mast cells and, in some cases, induce these cells to release mediators.¹¹ In such settings, it appears that the active IgE antibodies themselves can induce FcεRI aggregation. For one of the monoclonal mouse IgE antibodies with this property, this may reflect the molecule's ability to assume at least 2 distinct isomeric conformations in its antigen binding site, one of which can bind the known antigen and the other of which can bind, albeit with a lower affinity, a structurally and chemically distinct antigen.¹²

The extent to which these intriguing findings can be generalized to other rodent or human IgE antibodies remains to be determined. The same is true with respect to the clinical implications (if any) of the ability of IgE to enhance mast cell survival and/or secretory function in the absence of the antigen for which that IgE is known to have specificity. However, the ability of high levels of IgE to enhance mast cell and basophil surface expression of FcεRI and, in turn, the cells' secretory function on FcεRI aggregation does appear to have clinical relevance.¹⁰ The implication of these findings is that subjects with high levels of IgE, and therefore with high levels of expression of FcεRI on the surface of mast cells and basophils, have key effector cells of anaphylaxis (ie, mast cells and basophils) that are primed to be more exquisitely sensitive to antigen, and to release larger amounts of mediators in response to antigen challenge, than are those in subjects with lower levels of IgE.

Accordingly, the potential effects of anti-IgE therapy on the established ability of IgE to enhance IgE-dependent and antigen-dependent effector cell function, as well as on the possible ability of certain IgE antibodies to induce mast cell mediator secretion in the absence of known specific antigen,¹¹ must be kept in mind when evaluating the results of IgE-targeted therapeutic approaches, whether in subjects at risk for anaphylaxis¹³ or in patients with atopic asthma or other IgE-associated disorders.¹⁴ Indeed, the diverse anti-inflammatory effects of anti-IgE treatment that already have been reported in patients with allergic asthma or allergic rhinitis provide additional support for the central role of IgE in the development and maintenance of allergic inflammation.¹⁴

Although there has been impressive progress in understanding the IgE-dependent and mast cell-dependent initiation of episodes of anaphylaxis, those readers who

review this issue of the Journal in its entirety, including the report of a workshop on anaphylaxis held recently at the National Institutes of Health,¹⁵ will realize that several other important issues pertaining to our understanding of anaphylaxis, or to its effective management, are as yet unsettled. For example, it is not clear to what extent antibody isotypes other than IgE contribute to the expression of this disorder in human beings.² By contrast, it is well known that in mice, either IgE or IgG1 antibodies, acting via FcεRI or FcγRIII, respectively, can each induce potentially fatal anaphylactic reactions.^{2,16} The IgE-dependent mechanism, which involves mast cells, histamine, and platelet activating factor, requires much smaller amounts of antibody and antigen than the IgG-dependent mechanism, which involves macrophages and platelet activating factor.² Although most cases of antigen-induced anaphylaxis in human beings likely reflect activation of the IgE-dependent pathway (in that the disorder can be induced by tiny amounts of antigen and, at least in the case of peanut allergy, the threshold of sensitivity to the allergen can be ameliorated significantly in subjects treated with anti-IgE¹³), the IgG-dependent pathway may account for disease in subjects repeatedly exposed to large quantities of antigen (which, in rare instances, may even be anti-IgE antibody itself).¹⁷

Are mast cells and basophils the only significant cellular sources of mediators in anaphylaxis in human beings? As noted, work in mouse models as well as clinical observations strongly suggest that the answer is no.² On the other hand, to date, the only blood test generally accepted as both relatively specific and practically useful for diagnosing anaphylaxis is that which measures serum tryptase, a mast cell-associated mediator.¹⁸ That this test is of so little value in the evaluation of children with severe food allergy and food-related anaphylaxis¹⁹ represents just one reason to seek alternative informative (and, ideally, rapidly performable) diagnostic tests for the evaluation of such patients and others subject to this disorder.

There are other important unanswered questions as well. How can we explain, pathogenetically, the late sequelae of anaphylaxis observed in some patients?^{19,20} Why do only certain individuals develop this pattern of reactivity, and to what extent does this reflect genetic, as opposed to environmental, factors? Finally, what more can be done to discover improved treatments for this disorder and, in the area of public policy, to use effectively what we already know about the causes, management, and treatment of anaphylaxis to improve, and in some cases to save, the lives of those afflicted with this devastating condition? The recommendations of the Joint Task Force on Practice Parameters, as summarized in this issue,²⁰ represent an important contribution to this effort, as does the report¹⁵ of a workshop on anaphylaxis sponsored jointly by the National Institutes of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network, an advocacy group that has been active in this area.

The latter report should be of considerable interest to allergists and to specialists in many other disciplines in that it will reflect and discuss what was obvious to

participants in the workshop: there is a deeply felt need for very simple and useful guidelines for the diagnosis and immediate management of anaphylaxis (and those clinically similar anaphylactoid reactions elicited independently of IgE) that can be used by the diverse spectrum of caregivers who often are the first professionals to come in contact with the patient. This group includes first responders, such as emergency medical technicians, as well as emergency department physicians, pediatricians, general and family practitioners, internists, anesthesiologists, and nurse practitioners, in addition to allergists.

It is clear that members of different medical subspecialties in the United States do not currently agree on key aspects of the diagnosis and management of anaphylaxis (including which of the potentially susceptible individuals should be advised to carry self-injectable epinephrine, and how they should be advised about when to administer it²¹). This represents a significant challenge to the professional organizations that will be responsible for attempting to achieve consensus in this critically important area. After all, many patients who have episodes of anaphylaxis will first be seen by someone other than the patient's allergist, or may even be alone when the incident occurs.

From an international perspective, the situation is even more challenging. Participants in a recent international conference on anaphylaxis²² realized that, even among physicians trained in allergy, there can be significant differences among physicians from different countries in views, sometimes deeply held, on the classification, diagnosis, severity grading, and treatment of anaphylaxis. Indeed, there is no international consensus on the classification and nomenclature of anaphylaxis, especially when one considers those expressions of the disorder that may reflect the activation of mast cells and other effector cells independently of IgE.

By reporting that injections of extracts of the venom sacs of stinging insects (*Hymenoptera*) could essentially cure patients of fatal anaphylactic reactivity to the stings of such insects,²³ Mary Hewitt Loveless both pioneered the effective antigen-specific immunotherapy of anaphylaxis and foreshadowed the now vibrant field of immune tolerance. As discussed by David Golden²⁴ in this issue, venom immunotherapy remains the mainstay of the treatment of patients with anaphylactic reactivity to these allergens. Yet even though Loveless's important discovery was published almost 50 years ago,²³ insect venom-induced anaphylaxis remains the only form of this disorder for which allergen-specific immunotherapy is available.²⁴ Moreover, the mechanisms that account for immune tolerance in this setting, or that determine the duration of the protective effect, have not been fully elucidated.²⁴ Finally, we still cannot understand, let alone predict, why some venom-sensitive patients will develop anaphylaxis on being stung, whereas others will not.²⁴ In mouse models, IL-4 or IL-13 can exacerbate the effector phase of anaphylaxis, at least in part by increasing target cell responsiveness to vasoactive mediators.² Could a mechanism such as this contribute to the observation that subjects

with food allergy who also have asthma appear to be particularly susceptible to fatal anaphylaxis?²⁵ And will it be possible to devise improved diagnostic tests to identify those sensitized individuals who are at greatest risk for the development of severe systemic reactions to allergens, including fatal anaphylaxis?

Although venom immunotherapy can provide significant protection for insect venom-sensitive subjects,²⁴ and the initial results of using anti-IgE therapy in patients with peanut allergy appear quite promising,¹³ anaphylaxis unfortunately remains a major problem for many individuals, particularly those with food allergies. Moreover, despite much recent progress in the understanding of the pathogenesis, pathophysiology, prevention, and treatment of anaphylaxis, most tragically, some patients still die of this disorder. Even though there has been impressive progress in the understanding and management of anaphylaxis over the period of the last 100 years, there is much work still left to do.

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