

# Fluorescein-induced adverse reaction

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**Key words:** adverse reaction; anaphylaxis; fluorescein.

● SODIUM fluorescein is a commonly used agent to diagnose many ocular diseases (1, 2). Adverse reactions following its intravenous administration are rare. However, patients with adverse reactions to other drugs are referred to our service for study. The protocol for adverse reactions to fluorescein consists of performing a skin prick test with a 200 mg/ml concentration and interdermal reactions with 1/1000, 1/100, and 1/10 dilutions. A 50% glycerin saline solution and 1% histamine chloride are used for negative and positive controls, respectively. Whenever the skin tests are negative, a conjunctival provocation test with fluorescein is performed.

In the last 5 years, 335 patients have been referred to our service to exclude sensitization to fluorescein. Except for two cases that we will describe here, the study was negative and the provocation was also negative.

*Case A.* A 23-year-old woman who presented hypotension, respiratory distress, and hand edema with itching and sensation of warmth after administration of intravenous fluorescein required urgent medical care and treatment with intravenous antihistamines and corticoids. Hours later, the patient suffered facial angioedema. She had not undergone any previous fluorescein tests. She reported no personal history of adverse reactions to other drugs. Skin prick tests performed with sodium fluorescein were positive with a 5-mm papule.

*Case B.* A 75-year-old man who, after the administration of intravenous fluorescein, immediately presented intense respiratory distress and loss of consciousness required urgent medical treatment with epinephrine, serum therapy, and corticoids. The patient did not mention any previous angiographies. There was no significant personal history. Given the high risk of this patient, the prick test was performed with sodium fluorescein at a 1/1000 dilution (0.2 mg/ml), and it was positive with a 6-mm papule.

Adverse effects from the intravenous administration of fluorescein appear in 5% of the cases. The most frequent manifestations are nausea and vomiting, and serious adverse effects, according to different authors, are rare (0.05%) (2). The cases of death are estimated to be 1/222 000 angiographies (3).

The pathogenic mechanism of the adverse reactions is related to various unknown factors. Contrast media, including fluorescein, produce adverse effects due to activation of the complement and release of different mediators. It is known that fluorescein can cause the destruction of the vascular endothelium through factor XII and the coagulation system (4, 5), this being the mechanism that gives rise to some adverse reactions. Several authors consider the presence of an adverse reaction to a drug and a history of previous reactions to be predisposing factors. Thus, the ophthalmology department refers patients to us to exclude sensitization. In our cases, we observed that the previous skin tests done had no predictive value and that it was useless to perform them since the common reaction mechanism is not IgE mediated (1), and thus the tests were negative.

In the two cases presented, there was no history of an adverse reaction to a drug and the patients had not been administered fluorescein previously, such an administration, according to Kwiterovich et al. (2), being the most important risk factor for presenting a serious adverse reaction to fluorescein.

The two patients presented had an anaphylactic reaction, and the existence of positive skin prick tests suggests the existence of an IgE-mediated mechanism for which the sensitization route is unknown.

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## Degranulation in eosinophils in human, but not in mouse, airways

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**Key words:** allergic airways; eosinophil degranulation; human; mouse.

● ON the basis of original micrographs presented in their review in *Allergy* on allergic airway inflammation in the mouse, Hamelmann et al. (1) state that ">90% of eosinophils in the airways were activated" (degranulating). However, their qualitative evidence may not stand up to scrutiny, particularly when compared to the

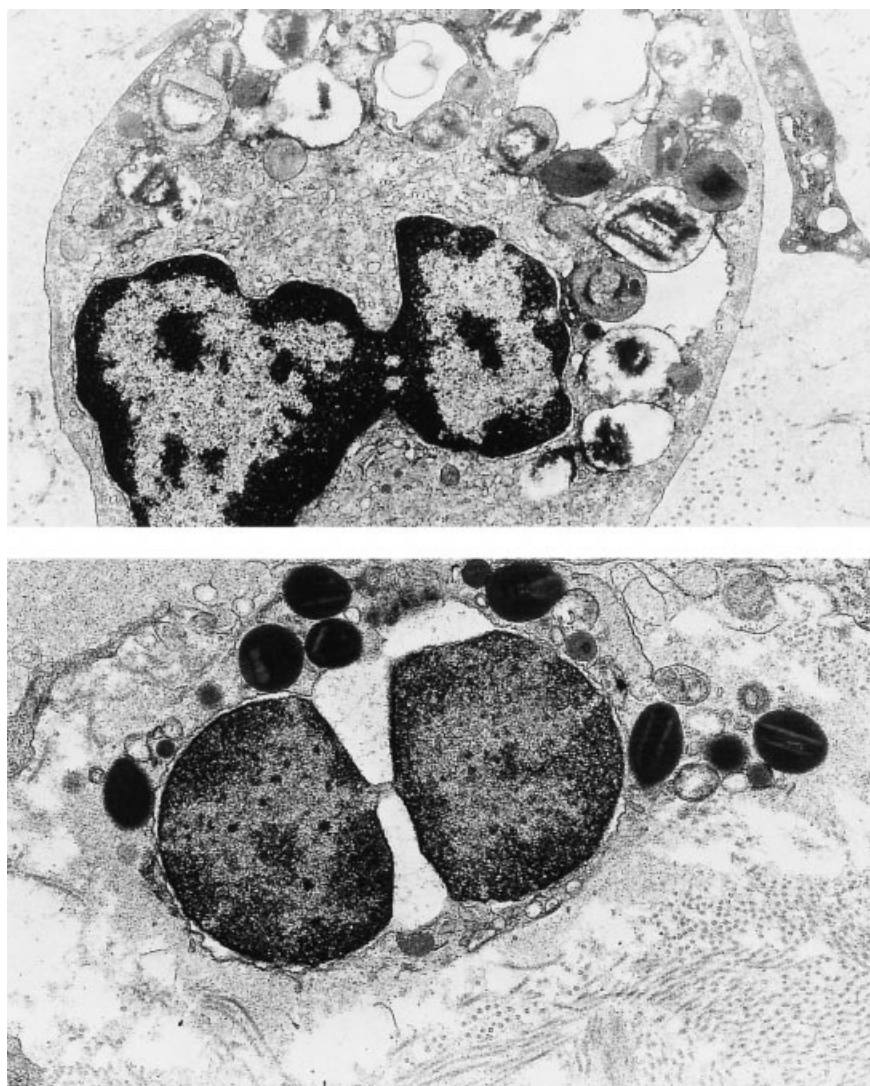


*Figure 1.* Transmission electron micrographs demonstrating eosinophils undergoing piecemeal degranulation (PMD) (above) and eosinophil cytolysis (ECL) (below) in human allergen-exposed airway mucosa *in vivo*. PMD occurs in viable cells exhibiting multiple morphologic changes in both the core and matrix of the specific granules. ECL is characterized by cell nuclei chromatolysis, rupture of the cell membrane, and spilling of protein-laden specific granules into the surrounding extracellular matrix. PMD and ECL are being assessed quantitatively in human airway diseases (4–6, unpublished observations).

conspicuous degranulation exhibited by human airway

eosinophils (see Fig. 1 and below). Moreover, quantitative data are missing, and other workers have failed to detect signs of eosinophil degranulation in mouse airways (2, 3).

Since acceptable immunomarkers of degranulating eosinophils are lacking, qualitative and quantitative data in this area

**Are *in vivo* observations in man clinically less relevant than data/concepts emanating from mouse models and cell cultures?**

have to be based on cell morphology (2, 4–6). Through piecemeal degranulation (PMD), granular contents are gradually released from eosinophils that remain viable (4, 5) (Fig. 1). PMD commonly occurs *in vivo* in allergic rhinitis, nasal polyposis, and asthma (4, 5, unpublished observations). Dramatic degranulation in these diseases is effected by eosinophil cytolysis (4–6), defined as chromatolysis, cell membrane rupture, and spilling of protein-laden specific granules into the extracellular matrix (Fig. 1). In moderate disease, a large proportion of the mucosal tissue eosinophils may be cytolytic (6). By

comparison, mouse airway eosinophils are exceedingly resistant to degranulation, even when repeatedly exposed to huge doses of allergen (2, 3). (See also Fig. 5 in Hamelmann et al. [1].) Contrary to the inference made by Hamelmann et al. (1), the occurrence of “pseudopods” and “unrounding of cells” in mouse eosinophils may have nothing to do with degranulation (cf Fig. 1) (4–6). Merely counting the number of specific granules may also be an unsatisfactory method to determine eosinophil degranulation (5).

The so-called airway hyperresponsiveness (AHR) determined in the current mouse

models, which lack asthma-like eosinophilic, microvascular, and epithelial abnormality (2), cannot automatically be considered relevant. Indeed, the term "AHR" should probably not be used interchangeably for human asthma and the mouse phenomenon (3). This view, again, deviates from the unreserved enthusiasm expressed by Hamelmann et al. (1): "The mouse provides an excellent model to investigate the contribution of individual components to the development of AHR." Clearly, "cutting edge" mouse data create attractive concepts, making us all wish that relevance did reside in the murine world of immunomechanisms. However, science may not be well served by uncritical application of hegemonic mouse paradigms to the capricious and poorly understood human disease complex that we call asthma (2).

Several *in vitro*–*in vivo* dichotomies may be found merely regarding the fate and modes of degranulation of airway eosinophils (2–6, abundant unpublished observations). For example, how can *in vitro* data/concepts regarding eosinophil exocytosis and

eosinophil apoptosis, respectively, become widely acknowledged "airway paradigms" when supporting human *in vivo* data continue to be lacking (4–6)? And how can such a striking *in vivo* mechanism as eosinophil cytolysis (4–6) be ignored by *in vitro* investigators? Such points of discussion are avoided; in fact, they may be effectively silenced. On a general note, it appears that current trends in asthma research reflect an imbalance between immunologic work/concepts involving mouse and *in vitro* cell phenotypes on the one hand and classical clinical research on the other (7). We fear the day will come when actual observations in real disease cannot be accepted because they cannot be made in current mouse models, or because they deviate from current standards of *in vitro* cell mechanisms. Perhaps we are already there?

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