

Human passive cutaneous anaphylaxis in the 21st century: Worth the risk?

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Key words: Passive cutaneous anaphylaxis, PK test, medical ethics

"In 1921, Otto Carl W. Prausnitz (Giles) (1876-1963) identified what was later called 'reagin,' now known to be immunoglobulin E (IgE) antibody, found in higher quantities in the serum of allergic individuals than in nonallergic individuals. Prausnitz and his colleague, Heinz Küstner (1897-1963), discovered that a serum factor from an allergic patient (Küstner) could transfer skin-sensitizing properties to another individual (Prausnitz). Twenty-four hours after injecting serum from Küstner, who was allergic to fish, into Prausnitz's skin, they injected fish extract into the same area. A wheal (edema)-and-flare (erythema) reaction appeared at the site of the antigen-antibody reaction. They realized that this could be developed as a sensitive, specific diagnostic method for identifying either an antigen or an antibody."¹ This test became known as the Prausnitz-Küstner (PK) test.

This skin transferring factor, referred to first by Coca (1875-1959) as "atopic reagin," was differentiated from a precipitant, which resulted in an antigen-antibody complex.¹ Reagin reacted with an allergen, as shown by the PK test. In 1967, Kimishiga and Teruko Ishisaka were the primary research investigators who demonstrated that the skin testing antibody or reagin was not IgA, as previously believed, but a newly isolated gammaglobulin, which they named IgE.² Concurrently, Hans Bennich and S. G. O. Johansson³ isolated an immunoglobulin they termed IgND from a patient with multiple myeloma, which was later confirmed to be the IgE molecule discovered by the Ishisakas.

In this issue of the *Journal*, Mose et al⁴ use the PK test to determine whether the serum level of peanut allergen-specific IgE and the oral challenge dose of peanut affect reaction time and wheal size in the IgE-mediated cutaneous PK test. Human

sera from 4 peanut-sensitive donors were used to test this hypothesis in 41 healthy nonallergic recipients. The authors found that an increase in either the peanut-specific IgE level or oral challenge dose of peanut in the PK recipient shortened the PK reaction time. They also found that a higher challenge dose of peanut increased the magnitude of the PK reaction.

What about using the PK test as used in the article by Mose et al?⁴ Although we cannot speak for all institutional review boards (IRBs) in the United States, most, if not all, IRBs, including that of the University of South Florida, would not today approve the use of a PK test for experimental purposes, regardless of the specifications of the protocol. Discovery of hepatitis B virus and other viruses during the 1960s and early 1970s made the US medical community seriously consider the risks taken when performing experimental PK tests on volunteers and on one another as younger physicians (including one of the authors [R.F.L.]).

Another question that must be addressed is whether the information derived from any study justifies the use of a test that potentially puts human subjects at risk. How much additional information does this study provide? It is recognized that there is, in general, a direct correlation between the degree of sensitivity and the allergen dose administered for IgE-mediated reactions: the greater the sensitivity and the higher the dose, the more intense the reaction. Likewise, the severity of a systemic allergic reaction, including anaphylaxis, is in general related to the degree of sensitivity and the dose of allergen administered. The studies by Mose et al⁴ confirm these concepts in the context of peanut-induced human allergic reactions.

However, the main question is whether current screening procedures for blood and blood products are sufficient to alleviate concerns about the safety of this test. A donor's medical history and molecular screening for blood-borne pathogens are the standard procedures for ensuring the safety of recipients. The list of blood-borne pathogens screened in donated blood varies from country to country but generally includes a common list of viruses (HIV-1/2, human T lymphotropic virus I/II, hepatitis B virus, and hepatitis C virus) plus other pathogens tailored to the most prevalent endemic infectious diseases. For certain human samples, the University of South Florida Institutional Biosafety Committee requires testing for several potential pathogens in addition to the typical blood-borne pathogens for research performed at animal biosafety level 1 to ensure the health of animal care workers. These additional agents of concern include *Mycoplasma* species, hepatitis A virus, hantaviruses (Hantaan, Seoul, and Sin Nombre), herpesviruses (herpes simplex viruses 1 and 2, human herpesviruses 6 and 8, varicella zoster virus, EBV, and cytomegalovirus), adenoviruses, human papillomaviruses 16 and 18, and lymphocytic choriomeningitis virus.

Although the medical history and appropriate molecular detection assays functionally screen out major potential pathogens, there is still the possibility that unscreened pathogens will be transmitted.

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Disclosure of potential conflict of interest: R. F. Lockey is a member of the *Journal of Allergy and Clinical Immunology*: In Practice Editorial Board and is a board member for Allergy, Asthma and Immunology Research; has consultant arrangements with Merck and AstraZeneca; is employed by the University of South Florida Morsani College of Medicine; has received payment for lectures from Merck and AstraZeneca; has received royalties from Informa Publishing; has received payment for development of educational presentations from Merck and AstraZeneca; and has received travel support from national and international congresses for presentations. M. N. Teng has received grants from the National Institute of Allergy and Infectious Diseases (P01AI112524), has a patent through the United States Patent and Trademark Office (US5,993,824), and has received travel support from the American Academy of Allergy, Asthma & Immunology.

Received for publication December 22, 2016; accepted for publication January 3, 2017.

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J Allergy Clin Immunol 2017;■■■:■■■-■■■.

0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2017.01.012>

There are viral infections that cause asymptomatic viremia (eg, Zika virus) that can be transmitted in a manner not captured by the medical history. Globalization of travel means that travelers arriving from different countries often meet in transportation hubs. Thus transmission of known or even unknown/emerging pathogens can occur in such settings. Even viruses that are prevalent within the population, such as herpesviruses (eg, EBV and cytomegalovirus), polyomaviruses (eg, JC, BK, and Merkel Cell virus), or small anelloviruses (eg, torque teno virus), can cause or enhance disease when injected into recipients.

As with all testing performed in human subjects, the risk/benefit relationship must be carefully weighed by both the physician-scientists and local and national regulatory agencies. The study by Mose et al⁴ was reviewed appropriately before performance, having received approval from their IRB and the Regional Scientific Ethics Committee and having followed the Danish blood safety directives.⁵ With these procedures in place, the risk of infectious disease transmission during PK testing was likely very small. However, the medical community in the United States has decided that the benefits of such tests do not outweigh the potential risks. Thus the PK test has been phased out as an assay for allergic sensitization.

There is one other point: many great discoveries have come from human experimentation, and many will be forthcoming in

the future. Individual investigators, institutions, and countries have to decide what is acceptable and not acceptable when performing experiments in human subjects. Codes of ethics governing such research require that all investigators consider the welfare of their study subjects versus the interest of science and society. The ultimate responsibility of any physician-investigator, as derived from the Hippocratic Oath, is “nil nocere” (translated as “do no harm”).⁶ This ideal should be our foremost thought when performing research on human volunteers.

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