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# Two-Midnight Rule: What We Need to Know

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# New Generation of the Poison Ivy Vaccine in Clinical Study

*by Robert E. Coifman, MD, Cathy F. Yang, Ph.D., and Sarah Klosek*

***NOTE:* Typographical errors in original published article are corrected in this copy.**

Medical research and education are thriving in New Jersey, with Rowan University as just one example of an institution were both are occurring with exciting results. The University recently announced $5 million in funding for the Rowan University Venture Fund to support early stage research. Earlier this year, the University received a $3.05 million grant from the Robert Wood Johnson Foundation to develop new health care delivery education and research programs. Additionally, US News & World Report has named Rowan University School of Osteopathic Medicine as one of the country's best medical schools for geriatric medical education. The impact of robust medical research and education opportunities available in New Jersey is demonstrated by the results of the collaborative efforts of New Jersey allergist, Dr. Robert Coifman, and Rowan University Professor of Chemistry, Dr. Cathy Yang.

In the summer of 2008, a 30 year old tree trimmer came to the Millville office of allergist Dr. Robert Coifman, seeking allergy management for recurrent severe poison ivy. He was unable to avoid it in the course of his work, and for the past several summers he needed continuous treatment with high doses of prednisone.

There had been commercial poison ivy vaccines from the 1950's into the 1980's but in the late 1980's they were all been pulled from the market because of inability to demonstrate predictable effectiveness in studies the FDA directed by Congress to require for continued licensure of allergy vaccines that had been approved before effectiveness testing was required.

While the old vaccines did not help enough patients enough of the time to pass the FDA's effectiveness test, they had definitely helped some patients, and they had never been shown to produce dangerous side effects. It seemed to Dr. Coifman that the risks of treatment with a home-made vaccine made from fresh poison ivy leaves would be less than the risks of taking high doses of prednisone for six months or more of every year, so he offered to try to make one. The patient gave his consent. Dr. Coifman then contacted Rowan Chemistry Prof. Cathy Yang to ask if she'd be interested in working together to make a poison ivy allergy vaccine, and she said yes. Dr. Coifman and his staff harvested fresh poison ivy leaves from a farm owned by one of his employees, and Prof. Yang and her associates turned it into their first generation allergy vaccine. Together they developed a quantitative poison ivy allergy patch test, with which they can measure sensitivity before treatment, measure response to treatment, and track response to treatment over time.

The allergens in poison ivy are a family of four similar chemicals called urushiols, collectively referred to as poison ivy urushiol. Poison ivy urushiol is not soluble in water but it will dissolve in vegetable oils, and in previous poison ivy vaccines it had been dissolved and injected in sterile corn or olive oil.

Vegetable oils are extremely difficult to sterilize if they are accidentally contaminated. Because of this, vaccines of poison ivy urushiol dissolved in vegetable oils had been manufactured in closed, totally germ-free production lines. It would be costly to set up a sterile, germ-free production line for the small quantities of vaccine needed for early phase clinical trials, and it would be both costly and difficult to modify the vaccine preparation process in a closed production line to make the changes they knew, they'd want to make, as they learned from ongoing experience. Coifman and Yang therefore decided to make vaccines by dissolving and injecting poison ivy urushiol in small volumes of ethyl alcohol (ethanol). Ethanol stings more than vegetable oil on injection but it's self-sterilizing, which made it possible to both make the vaccine, and modify the vaccine preparation process, using clean but not sterile technique in ordinary chemistry laboratory work-space.

Allergy vaccines can be designed to do either or both of two things. One is to produce desensitization, a temporary ability to tolerate the offending allergen that develops as the dose of vaccine is increased to a level shown to be effective, and that lasts as long as treatment is continued. Treatment should be daily, or no farther apart than every two to three days, with the maximum dosing interval needed to maintain the desensitized state depending on the allergy and the vaccine. Readers may have read or heard about clinical trials of desensitization for peanut and other food allergies, which have not produced perfect results, but have helped many patients with severe allergies to those foods.

The ideal goal of treatment with an allergy vaccine is to induce durable immunologic tolerance, which is as being

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on a biological email OK-list. The immune system learns in the process of immunization to accept and tolerate the target allergen in the same way that a healthy immune system tolerates one's own tissues, identifying it as fine without need for continuing vaccine treatment. Once durable immunologic tolerance is achieved, it typically lasts for months to years without need for ongoing treatment.

The most effective previously reported approach to durable induction of immunologic tolerance to poison ivy previously reported in response to poison ivy vaccines was in guinea pigs, not humans. A chemically modified poison ivy urushiol vaccine injected in corn oil produced partial tolerance, persisting one to two months after treatment. The tree-trimmer who was the first patient treated with Coifman and Yang's poison ivy vaccine developed complete clinical tolerance (no reaction to the same workplace exposures that had previously required months of continuous high dose prednisone) and became 100 times less sensitive by quantitative patch test. He retained both his clinical protection and his patch test response nine months after treatment, but lost clinical protection and his patch test sensitivity returned to his pre-treatment level 14 months after treatment. (At that time he changed his occupation for reasons other than poison ivy allergy, so he was not interested in re-treatment.)

Three other highly allergic patients also responded complete clinical responses to treatment, with 22 to 5000 times reduction in patch test sensitivity. In one, clinical and patch test protection were present at 9 months but lost by 12 months. The patient who became 5000 times less sensitive was still clinically protected, and remained 1250 times less sensitive than before treatment at four years. The third patient was lost to follow-up after 3 months. In terms of the amount of allergen needed compared to the weight of the patient, our vaccine in ethanol was 200 times as effective as the best previously reported poison ivy vaccine in corn oil.

However, our initial vaccine did not induce tolerance in patients who were less sensitive before beginning treatment and it also lost potency more quickly than we would like, despite refrigeration. It was also so dilute that we could not inject larger doses without injecting unacceptably large volumes of ethanol.

Prof. Yang designed a procedure to make a much more concentrated, purified and stable poison ivy urushiol vaccine, also in ethanol. It induced tolerance as well as the original. Dr. Coifman, who was mildly allergic to poison ivy before treatment, kept increasing his own dose of the purified vaccine to see if by increasing dose he could induce tolerance in himself, as a mildly allergic patient. He succeeded, but only at a high enough dose to produce hives lasting three months. Dr. Coifman did not have known contact with poison ivy to learn if he had clinical protection, but he was protected by patch test at 3 months and lost that protection by 16 months. The reduced effectivess of the purified vaccine suggested that something useful was lost in the purification process.

With a third vaccine, a mix of vaccine formulae #1 and #2, Dr. Coifman again induced tolerance in himself, this time at a dose whose only side effect was a temporary increase in the level of certain allergic cells in the blood. Dr. Yang then produced a 4th vaccine, as concentrated and as stable as purified vaccine #2, but containing everything present in her more effective but less stable vaccines #1 and #3. The first patient to receive this vaccine is currently being treated.

Coifman and Yang believe they understand why their poison ivy vaccines in ethanol work better than previous vaccines in vegetable oil. They believe the same mechanism can be adapted to vaccines for protein allergens, and have done very preliminary experiments to adapt the method to peanut. As they acquire more data on the safety and effectiveness of their poison ivy vaccines, they hope that they'll be able to interest a vaccine manufacturer in licensing their technology for commercial use. They are also generating candidate peanut allergy vaccines for animal trials. Hopes are that they will confirm their theory about how and why their ethanol-based vaccine works in animal models as well.

***About the Authors***

*Dr. Robert Coifman is a physician who treats patients through his solo practice - Allergy & Asthma of South Jersey. He is certified by the American Board of Pediatrics and the American Board of Allergy & Immunology. He is a fellow of the American Academy of Allergy, Asthma & Immunology, and the American College of Allergy, Asthma & Immunology, and he has served as a national scientific committee chairman and as a member of the national meeting continuing medical education program faculty for each of these two societies. Dr. Coifman can be reached at recoifman@gmail.com.*

*Dr. Catherine Yang is a professor in the Chemistry and Biochemistry Department at Rowan University. Dr. Yang's research includes drug discovery and development for indications such as cancer, diabetes, and allergies. During her tenure at Rowan, Dr. Yang received many academic awards including the Cottrell College Award of Research Corporation, the National Institute of Health AREA Grant Award, the Innovative Research Award of National Applied Chemical Laboratory, the National Science Foundation MRI Grant Award, and the Sigma Xi National Academy of Sciences Grants-in-Aid of Research. Dr. Yang can be reached at yang@rowan.edu.*

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