

Allergic Contact Dermatitis: The Future

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This article discusses the future of allergic contact dermatitis (ACD) diagnosis and management. Due to early landmark discoveries in this disorder, there is a knowledge base that can be refined. Improved patch-test technology, patch-test strategy, and patch-testing clinical relevance are emphasized. Other factors for improvement include complete ingredient identification on Material Safety Data Sheets, knowledge of the relationship of extracutaneous allergic disease to ACD, understanding of the evolutionary implications of ACD, increased chemical identification of allergens in publication, and enhanced knowledge of immunologic contact urticaria and irritant dermatitis syndrome. Further research into *in vitro* diagnostic methods, skin bioengineering tools, and ribonucleic acid diagnostic methods may lead to more precise and less invasive diagnosis of ACD. Development of national and international allergen banks and analytic chemistry laboratories would allow better documentation and epidemiology of allergens, as would collaboration between national and international contact dermatitis organizations via the World Wide Web. Finally, additional fellowships in contact allergy should produce more dermatologists equipped to face the complex challenges of ACD and develop solutions for ongoing questions.

PROGRESS is achieved by asking key questions and finding answers via observation, experimentation, and technology. Molecular biology began with the identification of deoxyribonucleic acid, followed by extensive experiments to elucidate its intricacies and complexities. It is impossible to predict the future despite our knowledge and understanding of the past and present.¹ Many factors are outside our control. Certainly, there was no way to foresee impressive contributions to general science such as mendelian genetics, darwinian evolution, and Einstein's physics, among others. Although the future of allergic contact dermatitis (ACD) is no exception to the laws of uncertainty, the following text discusses where the field may be headed and what barriers must be overcome to ensure scientific progress and improve clinical relevance.

Landmark Discoveries in ACD

A major development in ACD diagnosis—the creation of the patch test—is credited to Josef Jadassohn.² We have still not perfected the ramifications of this brilliant

technique, first described as a method for understanding mercury-induced eczematous dermatitis in a syphilis patient.³ Ideas for refining patch-test technology, methodology, and clinical relevance are the crux of our attempted prognostication.

Other contributors of major conceptual discoveries include the following:

1. Landsteiner and Jacobs. Their work suggested the relationship between chemical structure and allergenicity.⁴ They determined that allergens rely on conjugation with macromolecular carriers for the effective induction of skin sensitization.
2. Frey and de Weck. After removing lymph nodes from guinea pigs, they noticed that the guinea pigs did not develop allergy; thus, without lymph nodes, there was no ACD.⁵
3. Landsteiner and Chase. Using parabiotic guinea pigs, they elucidated the principles of passive transfer of delayed hypersensitivity (ie, if one guinea pig was allergic to a particular compound, the parabiotic animal also became allergic).⁶
4. Landsteiner and Draize. By performing repeat-insult patch testing in guinea pigs and humans (predictive testing), they determined which allergens would cause a reaction and which would not.⁴ We continue to refine this assay and its clinical interpretation.⁴

Improving Patch-Testing Technology

To further refine Jadassohn's patch testing, the following aspects might be addressed.

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Stability

Except for what is known of two dozen allergens,⁷ knowledge of allergen stability available to the public is *de minimis*. This is disconcerting because we may be applying commercial allergens without knowing how long they are biologically active. This information deserves to be open source, either on the allergen package insert or on the Internet. Bruze and colleagues determined an inadequate stability of isocyanates, which are widely used in industry and are productive of ACD and asthma.⁸ We suspect our clinic has misdiagnosed ACD from isocyanates on the basis of unstable allergens.

Identifying the True Allergen

We often assume that we know what chemical is causing a positive patch-test reaction. When patch-testing with paraphenylenediamine (PPD) yields a positive result, is the patient really allergic to PPD, or is the patient allergic to a metabolite and degradant produced on the skin after contact with PPD?⁹

Even when an allergen is identified (as in the case of PPD in hair dye), we remain uncertain about how the body processes it and the critical immunogenic steps involved.¹⁰ Furthermore, in the case of hair dye, allergens other than PPD may be overlooked. Knowledge of allergen structure, processing, and recognition by the body may allow structural modifications of common allergens to allow their use without inducing allergic reactions.

Natural products present a chemical identification problem because they may contain numerous allergens; thus, testing is nonspecific at best. This principle, brilliantly illustrated by Hjorth's work on balsam of Peru,¹¹ deserves to be followed up in regard to other complex chemicals. Lanolins represent such a challenge.

We need a clearer view of the chemical mechanisms of allergens and whether the true culprit is the allergen itself, a cross-contaminant, or a skin metabolite. Better definition of chemical structure as it relates to the clinical appearance of dermatitis would allow quantitative relationships for chemicals in commerce.¹⁰

The Next T.R.U.E.-Type Test

Relatively little patch testing is performed in the United States as compared to Europe. American dermatologists often use the Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test (Allerderm, Petaluma, CA) for its simplicity of application.^{7,12} Standardizing more allergens for Food and Drug Administration

approval is prohibitively expensive, leading to a lack of investment. A more efficient and convenient patch test (with predosed standardized allergens) is called for. It must be commercially viable and easily applied to the patient without technical assistance. Innovation is welcomed!

Commercial Availability of Serial Dilutions

Most patients are tested with one patch-test concentration.¹³ Fragrance mix I may be irritating and could cause a phenotypic dermatitis without an actual allergy present, resulting in misdiagnosis and unnecessary precautions.¹⁴ On the other hand, we screen for nickel at 2,500 to 5,000 parts per million (ppm) whereas some individuals may react to as little as 1 ppm. It is important to identify exquisitely sensitive individuals to inform them that even minimal and transient nickel exposure may produce dermatitis. Testing with serial dilutions permits the determination of just *how allergic* patients are. Not everyone reacts to the same concentration of a substance; some may react only to higher concentrations, thus allowing some exposure without phenotypic signs and symptoms. Clinical immunology should not be considered an "all or none" science; there are large interindividual variations in the amount of substance needed to elicit dermatitis.

Irritancy

Many allergens are marginal irritants as well, resulting in patch-test results that appear to be positive despite the lack of true chemical intolerance. Examples include formaldehyde, wool wax alcohol (lanolin), paraben mix, and carbamate. Occlusion also enhances the irritancy potential of some allergens.¹⁵ Future patch-test design should aim to identify methods of demonstrating allergenicity without false positives due to irritation. Advances in dermatopharmacokinetics might be used to advantage in this endeavor.^{16,17}

Patch-Wearing Periods

Patch tests may be accurately performed with a 24-hour application, yet the international standard remains 48 hours.¹⁸ This requires further investigation and discussion; patients would appreciate a shorter wearing time.

Application Periods

Evidence in animals and humans suggests that chemicals may need only 30 minutes of application for percutaneous

penetration.¹⁹ This would result in increased convenience for patients because patches worn on the back for 48 hours can be inconvenient and uncomfortable. Increased test concentrations might permit such an advance.

Patch-Test Banks

National, regional, and international patch-test banks should aid the patient, much as does the service of Klaus Andersen in Denmark.²⁰ These banks could distribute uncommon allergens to dermatologists for a flat annual fee and could also record response data to determine the frequency of sensitivity to rare or new allergens (thus serving as an early warning system).²¹

False-Negative Patch-Test Results

How do we explain the phenomenon of the patient who is clinically intolerant in a manner suggestive of ACD but is patch test negative to the given allergens? One (rare) explanation is compound allergy.²² Another (possibly more common) explanation is a false-negative result, presumably related to too low a concentration or to an inappropriate vehicle. Examples rarely reach publication.^{23,24} A systematic investigation of the maximal nonirritant concentration might help resolve this clinical dilemma.

Strategies for Improving Patch Testing

Special Series

How we examine data from patch testing is of critical importance. Special series deserve mention; they are ubiquitous, with series for everything from photographic chemicals to hair dyes and textiles. However, with the exception of the acrylate series, their validation is inadequately evidence based. Thus, positive results may not correlate with clinical relevance, and valuable allergens may be left out while low-yield allergens are included. A solution may be cooperative groups that use an evidence-based approach to determine which allergens should make their way to special series.²⁵ Clinical relevance deserves emphasis.

Intradermal Testing

Intradermal injection of an allergen is an ancient technique that is rarely used today.²⁶ A systematic reevaluation of when such testing is warranted would be appropriate. There are clinically relevant situations in which patch

testing yields negative results but intradermal injection yields positive reactions; situations involving corticoids and chromate are examples. The technique was abandoned prematurely and deserves reexamination in a systematic prospective manner. This represents another opportunity for cooperation between study groups.

Delayed Immediate Positive Reactions

Immunoglobulin E (IgE)-mediated wheal-and-flare reactions from prick testing may evolve into delayed cell-mediated immune reactions. With prick testing, a wheal-and-flare reaction is recorded in 20 minutes or so, but examination of the prick site on the next day may reveal a delayed erythematous papule—a reaction occurring after 8 hours. Thus, two lesion types may occur after prick testing: (1) immediate wheal-and-flare reactions and (2) late reactions due to cell-mediated immunity. Metals and corticosteroid contact allergies may present in this manner, increasing the value of delayed readings with these substances. We must clinically define what aspect of the clinical manifestations of protein allergens is IgE mediated and what aspect is cell mediated. Prick testing might even benefit from modification for the diagnosis of delayed hypersensitivity. A higher concentration of allergens and concomitant vasoconstrictors (eg, epinephrine) offer possibilities.

Improving the clinical reliability of commercial prick-test allergens is a *sine qua non* for improving clinical relevance. Poor correlations have been observed between commercially available food allergens as compared with actual allergens.²⁷ This may relate to heat instability of chemical or incomplete extraction.

Enhanced Material Safety Data Sheet Legislation

Improved Material Safety Data Sheet (MSDS) legislation should target the issue of secrecy regarding the ingredients of pharmaceutical, cosmetic, and consumer products. The withholding of information from MSDSs places patients and workers at risk. This area of public health needs leadership—a person or group that can fight for full disclosure of ingredients and advocate for patients. This goal has been accomplished for cosmetic labeling and should be extended to other product arenas.

Currently, if an allergen is less than 1% of a product, it does not need to be listed. Correcting this on a global scale (eg, listing all chemicals, major synonyms, and semiquantitative compositions) will aid patients.

Contact Allergy Versus ACD Disease and Extracutaneous Clinical Disease

“Contact allergy” describes the situation in which an individual has cell-mediated immunity as measured by patch testing or in vitro testing but does not develop a clinical disease. Intolerance to gold stents is an example: allergy to gold may not be expressed on the skin but may result in immunologic reactions to stents, resulting in restenosis.^{28–31} We must expand our knowledge of extracutaneous cell-mediated immunity (possibly unveiling groups of now-mysterious entities).

Evolutionary Implications of ACD

It is difficult to believe that human biology is accidental and that there is no evolutionary significance to ACD, but such significance remains hidden. We have an understanding of the disorder and its pathophysiology, but we do not know why it occurs. Understanding why could allow productive insights into the future of humans and our place in evolution. ACD might even provide evolutionary advantages.

ACD Analytic Chemistry Laboratories

We have incomplete knowledge of the chemistry of product allergies. In North America, the only chemical identification procedure commonly performed for ACD is the spot test for nickel. Patients with patch test–proven nickel allergy may use the spot test to determine if a piece of jewelry releases clinically significant nickel.

We desperately need an analytical chemistry center similar to those led by M. Bruze in Sweden, A. Lauerma in Finland, and T. Menne and colleagues in Denmark. It will take leadership and funding. (Possible sources for such funding include labor unions, industry, governments, and the World Health Organization.) This investment is cost effective. It is hoped that every region will have one such laboratory that can analyze allergen content in products and aid not only chemical identification but also prevention and management.

Clinical Relevance of Positive Patch-Test Reactions

Patch-test results may signify an immunologic response, but this may have little or no clinical significance.^{32–34} A multistep, methodical, and practical process is needed to determine this significance.

Currently, when a patch-test result is positive, we enlarge the patient’s history. This approach may aid in

distinguishing whether a response is an allergen or irritant. We ascertain (1) whether the appropriate irritant controls are available, (2) whether the morphology is that of ACD, (3) whether the patient was ever exposed to the chemical, and (4) a clinical course when the chemical is removed.³⁵ Furthermore, if the patient is reexposed to the putative allergen without being patch-tested (via a provocative use test), does such exposure reproduce the disease? Clinical relevance algorithms have been offered by Marrakchi, Lachapelle, Ale, and Hostynek.^{32–35}

Enhanced quantitative understanding of clinical relevance would allow mathematical handling to determine the probability of a true clinical allergy, given a positive patch-test result. Probability mathematics would add credibility to diagnosis. A uniform approach with appropriate follow-up in a large series of patients could pave the way for probability theory and databases to determine the likelihood of patch test–related clinical relevance.

Contact Allergy Certification and Fellowship

Certification by the American College of Mohs Surgery required 75 documented cases, yet any physician can patch-test and prick-test allergy patients, with no training. We propose a contact allergy fellowship program. More than 500 proctored cases could impart a solid foundation, and the fellowship could consist of 6 to 18 months of training. The United States may be one of the weaker Western nations in terms of patch-test training, and perhaps certification in contact allergy could provide a partial solution. Germany currently has such a training and certification process. Funding may be from the National Institute for Occupational Safety and Health, industry, the American Academy of Dermatology, the Personal Care Products Council, the International Fragrance Association, and trade groups and unions. The stipend for such a fellowship could range from \$25,000 (US) to \$50,000 (US) per year, an investment that should rapidly provide societal dividends.

Chemical Identification of Allergens in Publication

Most scholarly publications on ACD do not discuss the fundamental chemistry of ACD (asking, for example, what chemical caused the reaction). It is insufficient to have generic terminology without specific chemical identification. Physicochemical information should be included and discussed. Fregert provided such a precise template a generation ago.³⁶ Leadership—in terms of editors and reviewers—hopefully will bring us into conformance.

Irritant Dermatitis Syndrome

Irritant dermatitis (ID) is not as simple as some dermatologists and toxicologists believe. More than 10 phenotypic variants should be recognized by dermatologists and allergists. Improving knowledge of these would reduce the odds of misdiagnosis as allergy.³⁷ Further research in ID may result in better diagnosis of this entity.

From a public health standpoint, multiple dosing and cumulative application of a product should be examined by pharmacologic and cosmetic companies during testing, to reduce irritancy. Determination of the IT-50 (the estimated dose that produces a threshold reaction in 50% of the population) of a compound and subsequent extrapolation of the zero value (the non-irritating dose) via a graphic approach could prove particularly useful.³⁸

Skin Bioengineering

Many standardized and readily utilized instruments measure skin function (eg, transepidermal water loss, conductance, and capacitance). Determining how to use them clinically would make possible a more definitive approach to treating ACD. (For instance, currently we may state that a patient is 50% better after our intervention, but this is typically a rudimentary estimate at best; it assumes that we remember the previous morphology perfectly.) We might make our knowledge of irritant dermatitis and ACD more precise clinically by measuring variables with such instruments. Clinical studies and practice could reap the benefits of such a scientific approach. Patch-test scores and qualitative assessments (eg, the designation of “severe”), for example, are crude measurements, whereas bioengineering instruments provide efficient and often linear metrics. Incorporating them into clinical practice would permit patients to be followed quantitatively, not just qualitatively.

In Vitro Diagnostic Methods

We seek a clinically equivalent in vitro test for ACD, as is the radioallergosorbent test for IgE disease. An in vitro test for cell-mediated immunity is possible and could be accomplished experimentally, perhaps via peptide reactivity measurements.^{39,40} An award should be offered to encourage such a clinically relevant and practical assay! Ultimately, patients could give a small amount of blood for an accurate diagnosis; with modern molecular medicine, this is a possibility.

Diagnosis of ACD with Ribonucleic Acid from Tape Stripping

Ribonucleic acid (RNA) obtained from tape stripping or skin washes could be used to diagnose ACD. In molecular biology, RNA assays from skin cells can be performed quickly with kits. This could result in diagnosis of ID and ACD on the basis of RNA.⁴¹

Additionally, once the genetic code of a patient with ID or ACD is elaborated, therapy can be optimized with pharmacoepigenetics (a new field in pharmacology), which may help to elucidate interindividual differences in drug response.⁴²

Immunologic Contact Urticaria

Immunologic contact urticaria is an underserved diagnosis, especially given its ability to kill.⁴³ We need efficient methods to identify the disorder and to determine the quantitative structure-activity relationships (QSARs) of the chemicals most likely to produce it. Improved knowledge of this entity may increase our understanding of other disease processes, such as immunologic asthma, and could result in better labeling of problematic chemicals.

Dermatotoxicology

Dermatotoxicology could be the subject of an entire article, but a few points are worth mentioning here. First, publishing lists of chemicals that produce nonimmunologic contact urticaria (NICU) would aid patients, as would determining which chemicals are clinically comedogenic and acnegenic in humans. Using the IT-50 principle mentioned previously, we could ascertain the appropriate concentration of a chemical that would prevent NICU or acne.

World Wide Web

The World Wide Web holds endless possibilities for ACD knowledge refinement and management. It might focus on international allergen alternatives for health care workers and patients. It could bring together contact dermatitis groups (eg, the International Contact Dermatitis Research Group, the North American Contact Dermatitis Group, and the European Environmental Contact Dermatitis Research Group) for collaboration in ACD management.²⁵ Up-to-date databases of allergens and diagnostic methodology could be instantly available for all. Furthermore, groups should continue to work together to correct

discrepancies (eg, each group's use of different concentrations of the same allergen). Special-interest groups could also be formed for examining various allergens (metals, preservatives, etc).

Conclusion

Jadassohn would be delighted to observe the last century's progress! Some points noted here might accelerate the development of clinically useful and relevant information. If but a few readers focus and collaborate on these points, tomorrow will be better for patients.

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