Immunotherapy of allergic contact dermatitis

The term 'immunotherapy' refers to treating diseases by inducing, enhancing or suppressing immune responses. As allergy is an excessive, detrimental immune reaction to otherwise harmless environmental substances, immunotherapy of allergic disease is aimed at the induction of tolerance toward sensitizing antigens. This article focuses on the historical developments, present state and future outlook for immunotherapy with haptens as a therapeutic modality for allergic contact dermatitis. Inspired by the effectiveness of immunotherapy in respiratory allergies, attempts were undertaken at curing allergic contact dermatitis by means of controlled administration of the sensitizing haptens. Animal and human experiments confirmed that tolerance to haptens can be induced most effectively when the induction of tolerance precedes attempted sensitization. In real life, however, therapy is sought by people who are already sensitized and an effective reversal of hypersensitivity seems more difficult to achieve. Decades of research on *Rhus* hypersensitivity led to a conclusion that immunotherapy can suppress *Rhus* dermatitis, however, only to a limited degree, for a short period of time, and at a high risk of side effects, which makes this method therapeutically unprofitable. Methodological problems with most available studies of immunotherapy of contact allergy to nickel make any definite conclusions impossible at this stage.

KEYWORDS: allergic contact dermatitis allergy vaccination ▪ contact allergy ▪ contact eczema ▪ contact hypersensitivity ▪ hapten ▪ hyposensitization ▪ immunotherapy ▪ nickel ▪ *Rhus* ▪ tolerance induction

Radoslaw Spiewak

Department of Experimental Dermatology & Cosmetology, Faculty of Pharmacy, Jagiellonian University Medical College, ul. Medyczna 9, 30-688 Krakow, Poland
Tel.: +48 601 224 813
Fax: +48 124 166 262
spiewak@onet.eu

"A striking feature of the literature on Rhus *prophylaxis is the contradictory nature of many reports. Students of the subject hold diametrically opposed views. Some achieve remarkable results which are just as remarkably denied by others."*

– Albert M Kligman (1958)

Immunotherapy of allergic contact dermatitis (ACD) has tantalized allergists since the beginning of the 20th century. The term immunotherapy refers to treatment of disease by either inducing/enhancing or preventing/suppressing an immune response. As contact allergy is an excessive immune reaction to otherwise harmless environmental substances (haptens), immunotherapy of ACD should be aimed at preventing or suppressing immune response. The term 'tolerance' is used to define a state of unresponsiveness to antigen that occurs under circumstances where nontolerant individuals mount an immune response [1]. Depending on the status of a person, this may be achieved through: induction of immune tolerance to prevent sensitization; desensitization to eliminate existing hypersensitivity to a hapten or hyposensitization to reduce existing hypersensitivity to a hapten. This article will focus on the historical developments, present state and future outlook for immunotherapy of ACD.

Allergic contact dermatitis

Allergic contact dermatitis (synonym: allergic contact eczema) is inflammatory skin disease that develops in a person hypersensitive to a low-molecular-weight chemical (hapten), following exposure to this hapten. The diagnosis of ACD is based on clinical symptoms of dermatitis, positive results of patch tests in which suspected haptens are applied to the skin under controlled conditions, and a confirmation that one or more haptens eliciting positive patch tests are indeed present in patient's surrounding and are responsible for current relapse of the disease (clinical relevance) [2,3]. At present, there are no routine laboratory tests for the detection of contact allergy [4,5].

Haptens are too small (<500 Da) to be recognized by the immune system, thus they are not immunogenic *per se*. Immunogenic, however, can be the haptens' complexes with body's own proteins. Strong (mainly covalent) chemical bonds with haptens distort the spatial conformation of endogenous proteins to such extent that these are no longer tolerated as 'self'

but can induce immune reaction. The fact that these hapten–protein complexes are presented to naive lymphocytes through antigen-presenting cells (APCs) migrating from the skin, and the process of antigen recognition takes place in the local skin draining lymph nodes seems to determine the future skin-homing of emerging effector and memory lymphocytes [6–9]. It is important for the present review to keep in mind that while the induction of ACD has to occur via the epidermal route, subsequent elicitations of the disease in already-sensitized subjects may follow systemic exposure to the hapten (e.g., via oral or parenteral route). This situation, referred to as systemic ACD is an important point to observe while discussing the attempts to 'tolerize' patients with ACD by oral, intravenous or subcutaneous administration of haptens [10].

The hard job of immune tolerance

Each day, we are exposed to hundreds of haptens, yet only some people will eventually develop hypersensitivity to just one or a few haptens during their lifetime. This demonstrates that tolerance is the preferred way of action. Immune tolerance is not a mere act of not responding to antigens – this is an active process mediated by specialized subsets of antigen-specific lymphocytes [11–13]. The mechanisms deciding why one person becomes hypersensititive to a hapten, while most of us remain tolerant, are unclear. Factors that may influence the final decision between 'ignore' or 'react' include a coexistence of irritation or inflammation ('danger signals'), coexposures (adjuvants or carrier protein), previous exposures (e.g., exposure to superantigens anergizes experimental animals to subsequent antigen exposure), previous UV irradiation, and finally the site and route of primary exposure [1,14–17].

Hapten immunotherapy: the origin of the idea

The idea of hyposensitizing to haptens started from the practical need of helping patients with ACD, who could not avoid the exposure or needed to be exposed to their offending hapten (in case of required therapy). It's roots seem to be in the ideas of homeopathy that was very popular at that time ('fight similar with similar') [18], and anecdotal reports of American Indians avoiding *Rhus* dermatitis by chewing the leaves of the plants [19], which could not be confirmed by later systematic research [20]. Further inspiration seems to have come from early reports about successful therapy of hay fever by means of allergy vaccination [21,22]. The attempts at expanding the experience from hay fever onto dermatitis seemed justified to early allergists, who only decades later became aware of major mechanistic differences between the immediate and delayed-type allergy [23]. Further developments seem to present a rather unfortunate sequence of happenings, starting from a series of uncontrolled therapeutic trials with patients' and doctors' wishful thinking as the only outcome measure. These trials were soon followed by animal experiments that demonstrated that tolerance to haptens can indeed be induced, which was regarded as a scientific proof of the concept, irrespective of the fact that circumstances in animal experiment substantially differed from the situation of patients: in animal experiments, tolerance could be most successfully induced before or in the early phase of the attempted sensitization, whereas therapeutic trials were undertaken in people who were already sensitized. This difference went somewhat ignored by early proponents of hapten immunotherapy. A few decades later, epidemiological observations turned again the attention of allergists to the fact that the sequence of events might have been here the key factor.

Making animals tolerant to haptens

In 1929, Sulzberger published results of experimental study on the prevention of hypersensitivity to neoarsphenamine, an arsenic-containing drug for syphilis known as frequent cause of drug-induced dermatitis. In this well-designed experiment, guinea pigs were sensitized by a single intradermal injection of the drug. In the majority of animals, inflammatory reaction appeared within 2 weeks at injection site; moreover, strong inflammatory reaction developed in all following the second injection administered 1 month later. By contrast, no hypersensitivity reactions were observed in animals that received intracardial injection (systemic administration bypassing the skin) of neoarsphenamine 1 day after the first intradermal injection [24], which although somewhat weaker, was still demonstrable 2 months later. This protective effect did not occur when the intracardial injection was done 14 (instead of 1) days after first intradermal injection, suggesting that protection is only achievable during the induction phase of hypersensitivity. In extending Sulzberger's research, Chase demonstrated that induction of contact hypersensitivity to

dinitrochlorobenzene and trinitrochlorobenzene (picryl chloride) may be prevented by prior feeding guinea pigs with respective haptens (oral contact), he also demonstrated that such tolerance is hapten specific and long lasting (for at least 13 months) [25]. These observations were later confirmed by Coe and Salvin [26], altogether showing that contact hypersensitivity to haptens is less probable to develop if the skin contact was preceded or immediately followed by an extracutaneous exposure to the same hapten, which seems to divert the developing immune response in some way. From the present perspective, a possible explanation would be that this protective effect occurs in the phase when the newly developing effector cells are assigned to target organ, which is manifested by the appearance of homing antigens and chemokine receptors on the cell surface [27,28].

Chase was first to describe a seemingly paradox situation: in case of some haptens (e.g., picryl chloride) resistance to contact sensitization could be induced by applying (once or a few times) this very hapten to the skin [25]. This phenomenon was also studied by Moore in 1944 (results cited and discussed by Sulzberger and Baer [29]), who demonstrated in guinea pigs that epicutaneous exposure to undiluted mustard gas made the animals more resistant to subsequent sensitization attempts with the diluted (1:1000) hapten, as compared with animals that were previously not exposed. Lowney, using yet another experimental protocol in guinea pigs confirmed that epicutaneous application of diluted *p*-nitrosodimethylaniline (NDMA) and chlorprothixene made the animals less susceptible to sensitization by intradermal injection of the respective haptens [30].

Until that moment, the researchers were occupied mainly with experimental haptens (potent sensitizers) and drugs known as inducers of cutaneous adverse reactions. These haptens, however, were of relatively little relevance to real life. Therefore, researchers moved on to nickel that is the most frequent cause of contact allergy in humans [31]. A series of studies from Scheper's group demonstrated that feeding guinea pigs or mice with nickel- or chromium-containing food could prevent experimental induction of contact hypersensitivity to respective haptens [32–35]. Ishii *et al.* showed that resistance against skin sensitization to nickel is proportional to nickel concentration in drinking water administered to guinea pigs and the duration of the oral exposure [36], which later was also confirmed in mice [37]. The protective effect of oral exposure, however, may be abolished by previous, nonsensitizing skin exposure to nickel or chromium [38]. Also local administration of IL-12 (but not of IL-2, IFN-γ or GM-CSF) to the site of attempted epicutaneous immunization results in a breach of the orally-induced tolerance and full recovery of reactivity to haptens [39]. Nickel-specific suppressive T cells that emerge following oral or intraperitoneal administration of nickel can be used for transferring specific tolerance to previously nonexposed mice, a phenomenon referred to as 'infectious tolerance' [40,41]. The development of oral tolerance seems to depend on antigen presentation to $CD4^+$ T cells via the MHC class II pathway, as in mice depleted either of MHC class II molecule or $CD4^+CD25^+$ T cells, oral feeding with DNFB primes hypersensitivity instead of inducing tolerance to this hapten [40,42,43]. Using urushiol sensitization model in guinea pigs, Ikeda *et al.* demonstrated that the induction of immune tolerance was least effective in case of epicutaneous hyposensitization, better in oral administration of the hapten, and most effective in case of combined epicutaneous and oral exposure [44].

Hypothetically, the conflicting information about primary hapten contact sites (e.g., oral vs skin) might interfere with the development of hapten-specific lymphocytes through either halting the development of effector lymphocytes, skewing their phenotype toward regulatory lymphocytes, or directing effector cells to homing organs other than skin. If the last scenario was true, initial oral exposure would probably direct the emerging antigen-specific effector lymphocytes to mucosa, with the result that after subsequent skin exposure to the hapten, specific effector lymphocytes would migrate and initiate inflammation in the mucosa, not in the skin. Unfortunately, there is no mention in the published reports about checking for mucosal lesions of the exposed animals. In summary, animal experiments have confirmed that the development of contact hypersensitivity can be prevented by a preceding oral or parenteral administration of the hapten and, in some cases, also by a cutaneous exposure to defined concentrations.

Animal versus human

Undoubtedly, there are many immunological differences between laboratory animals and humans. Owing to legal and ethical

restrictions on human experiments, we will not be able to confirm in humans many of the previously published results of mouse or guinea pig experiments. However, results of a few human studies were published before the introduction of these restrictions. In 1941, Shelmire reported on a boy with recurrent poison-ivy dermatitis, in whom tolerance was achieved through repeated patch testing with increasing concentrations of poison ivy oleoresins at 4–7-day intervals for a period of 6 months. At the beginning, he reacted to a 1:5000 dilution of the oleoresins, while at the end of the trial, he reportedly not only tolerated the dilution of 1:10, but also the rubbing of his body with *Rhus toxicodendron* leaves [45]. Kligman has confirmed this observation experimentally in a group of eight volunteers; however, he also stressed on this occasion the impracticality of such 'therapy': it required over 300 applications of 3-n-pentadecylcatechol (PDC, the sensitizing compound of *Rhus* resin) over 9–11 months and caused initial aggravation of the symptoms after each increase of the dose [46]. It appeared that this kind of epicutaneous hyposenstization (perhaps via induction of a sustained refractory phase of ACD), although effective, seemed less tolerable than the disease itself.

In 1969, Epstein and coworkers started an experiment on inducing tolerance to urushiol through intramuscular injections to children previously unexposed to poison ivy or poison oak. For this purpose, they administered urushiol in olive oil 4 mg/ml, four intramuscular injections of 1 ml at weekly intervals to nine subjects aged 8–15 years. Six nontreated children of same age served as the control group (no injections). After 1 week following the last injection, an attempt was undertaken at sensitizing the children to urushiol oil. Only one in nine treated children, and five out of six controls succumbed to the sensitization ($p < 0.01$), which confirmed that also in humans the development of hypersensitivity via skin contact can be indeed prevented by preceding parenteral administration of the hapten. This study was terminated in halfway due to retraction of its ethical approval [47]. Using DNCB, a strong sensitizer that is not present in everyday environment, Lowney has confirmed in humans that oral exposure (buccal painting) decreased the degree of sensitization upon skin exposure: eight out of 17 individuals treated with prior buccal exposure could not be sensitized by subsequent skin application, as compared with only one resistant person out of 25 controls [48].

Epidemiological observations

Nowadays, most of the aforementioned experiments would be unacceptable from ethical point of view. A still acceptable way of verifying extrapolation from animal experiments to humans are the epidemiological studies. There are a couple of real-life situations that seem to confirm the prophylactic effect of oral exposure against the development of contact hypersensitivity. The studies analyzing these situation will be discussed from straightforward to more complex.

Primary oral versus skin exposure to urushiol

Approximately 50–80% of the general population of the USA may be allergic to poison ivy and poison oak [47,49]. The responsible sensitizer is urushiol (3′,5′-pentadecylcatechol) present in plants of the *Anacardiaceae* family, including poison ivy, poison oak, mango, cashew nut and ginkgo, which accounts for cross-reactivities between these plants. Hershko *et al.* reported on an epidemic of mango dermatitis among young Americans employed as mango pickers in Israel [50]: all subjects with mango dermatitis were visitors from Northern California, where exposure to poison ivy and poison oak is common, they also stated that they had never eaten mango previously. By contrast, none of the Israelis working in the same mango farm complained of any skin problem. In Israel, there are no *Rhus* plants while mango is a popular fruit, suggesting that Israelis were first exposed to urushiol via oral route that induced tolerance, whereas the Americans first encountered urushiol from *Rhus* through the skin that led to the development of contact hypersensitivity. Following identical skin exposure to urushiol from mango, the 'orally tolerized' Israelis did not develop any skin problem, while the epicutaneously sensitized Americans did. Similar phenomenon was observed in Hawaii: in a series of 90 consecutive patients with mango dermatitis, immigrants amounted to as many as 89% [51].

Primary oral versus skin exposure to nickel

A real-life situation in humans that resembles the aforementioned animal experiments with blocking development of cutaneous hypersensitivity through previous oral exposure to haptens is the influence of orthodontic treatment and of body piercing on the development of contact hypersensitivity to nickel.

Piercing and wearing nickel-releasing jewelry is a well-documented cause for early development of contact allergy to nickel [52,53], and may be viewed as an 'epidemiological analogy' to experimental skin sensitization of animals. A ban of nickel-releasing earrings in Denmark resulted in rates of nickel allergy among girls falling from 17.1 to 3.9% [54]. Similar EU-wide 'Nickel Directive', being in full force since 2001, seems to have failed at protecting the European consumers, as still 15–18% of earrings purchased in 2010 in London and Warsaw released nickel in amounts capable of inducing contact allergy [55,56]. In the USA, where there are no restriction on nickel content in consumer products, nickel allergy affects 35.8% of female patients under the age of 18 years [57]. This means that the sensitization to nickel continues on a massive scale in many countries. The second crucial part for this epidemiological observation is the wide use of orthodontic appliances that are mainly made of nickel-containing (and -releasing) alloys, which means a constant oral exposure to nickel. Based upon previously discussed animal experiments, one would expect lower prevalence rates of nickel allergy among those people, who had their dental braces before piercing, than among those who had piercing first. There are several epidemiological observations in favor of this hypothesis. Todd and Burrows studied 294 Northern Irish patients: the frequency of nickel allergy among those in whom orthodontic treatment preceded ear piercing was 25% compared with 36% among those who had no orthodontic treatment before piercing. They interpret the results as supportive of the view that oral hapten contact may induce immunological tolerance [58]. Even more convincing were observations of 417 Finnish girls undergoing orthodontic treatment: none of the girls who were treated with fixed orthodontic appliances before ear piercing showed hypersensitivity to nickel, in contrast to 35% of the girls who first experienced ear piercing [59]. Among Danish girls, these figures were respectively 2.1 versus 22.5% [60]. There are no observations about the dynamics of Ni allergy among those receiving dental braces after developing the allergy, although a hint can be found in a recent study by Johansson *et al.* demonstrating data from a longitudinal observation of 30 female patients undergoing orthodontic treatment with appliances containing 8–50% nickel, who were patch tested to nickel twice with a 1-year interval. Seven turned out to be patch test-positive, of whom two became negative during the study period, and one patient turned from negative to positive, indicating that under constant oral exposure to nickel, there may occur disappearance (or suppression) of a detectable skin hypersensitivity to the hapten, however, new sensitizations may also develop [61].

Altogether, the above studies indicate that application of dental braces (oral nickel exposure) prior to ear piercing (cutaneous nickel exposure) is associated with a reduced prevalence of nickel allergy. Although these data seem quite convincing, one should keep in mind that in contrast to controlled animal studies, piercing is not an exclusive way of acquiring nickel allergy, neither are dental braces the only source of oral nickel. Moreover, the above studies were not corrected for a crucial determining factor (i.e., the actual nickel content and release from the dental braces worn by the study subjects). In the aforementioned animal studies, the protective effect seemed proportional to oral nickel exposure. The release of nickel from stainless steel orthodontic appliances amounts to less than 0.13 µg/cm^2/week [62].

Intramuscular versus skin exposure to thiomersal

Organic mercury compound thiomersal (synonyms: thimerosal and merthiolate) is used as a preservative in vaccines, cosmetics and other easily spoiling products. As thiomersal-preserved vaccines used to be administered in early infancy, to many of people these intramuscular injections were the first encounter with the hapten, creating situation resembling the aforementioned Epstein's experiments on inducing immune tolerance by intramuscular injections of urushiol [47]. Indeed, despite the previous massive vaccinations with thiomersal-containing vaccines and its broad use as disinfectant and preservative for external drugs and cosmetics, very few cases of ACD to thiomersal were observed. In a study from the North American Contact Dermatitis Group (NACDG), thiomersal was the fifth most common sensitizer (positive patch test in 10.9% tested); however, it was considered relevant for present dermatitis only in 16.8% of these patients – the lowest rank of relevance among all 50 haptens in the NACDG test series [63]. Assuming that owing to its biological activity, thiomersal (as with many other preservatives) is a frequent skin senstitizer, a possible explanation for this low frequency of clinical symptoms despite high sensitization rates may

be the intramuscular route of first exposures. On the other hand, after withdrawal of this preservative from most consumer products, vaccines seem now the major source of thiomersal exposure with little everyday exposure that would give the chance to assess the clinical relevance of the sensitization. In a recent study of Polish children and adolescents with chronic or recurrent eczema, positive patch test to thiomersal was found in 11.7% of children (7–8 years of age) and 37.6% of adolescents (16–17 years of age) [64]. These differences reflect changing exposure patterns: the adolescents have received six thiomersal-preserved vaccines during their life course, with the last immunization taking place 2–3 years before the mentioned study. Younger children received only four thiomersal-preserved vaccines, with the last one applied 5 years before the study (further immunizations were performed with new thiomersal-free vaccines). This reinforces the notion of the main route of sensitization being through intramuscular vaccinations. Despite positive patch test, the patients tolerate well further thiomersal-preserved vaccines provided these are administered intramuscularly [65]. Among 45 patients with positive patch tests to thiomersal who were challenged with subcutaneous administration of this hapten, one patient developed generalized eczema and four reacted with local eczematous reaction; nevertheless, 40 patch test-positive patients remained tolerant to subcutaneous injection of the hapten [66]. On the other hand, there are data indicating a higher frequency of contact hypersensitivity to thiomersal among patients with chronic eczema: when comparing the aforementioned positivity rates among Polish children and adolescents with chronic eczema (11.7% in 7–8-year-olds and 37.6% in 16–17-year-olds in 2009 [64]) with samples from the general Polish population (8% among 13–15-year-olds in 1999 [67] and 18.5% among 18–19-year-olds in 2002 [68]), it becomes apparent that despite the partial withdrawal of thiomersal-containing vaccines that took place between these studies, the sensitization rates among children with eczema are 1.5–2-times higher than in the general population, which would indicate that thiomersal hypersensitivity might be of some importance in ACD. Altogether, the elicitation of clinical ACD to thiomersal seems influenced in some way by a complex and not-yet-understood interplay between the primary and present routes of exposure.

There may be an explanation alternative to the hypothesis of tolerance to thiomersal resulting from primary intramuscular exposure. The low incidence of thiomersal dermatitis despite high rates of positive patch tests might also be due to a high rate of false-positive patch tests: Typical thiomersal concentration used for patch testing is 0.1%, which is at least tenfold higher than concentrations in preserved products (range: 0.001–0.01%). This possibility of false positives due to a too-high test concentration seems supported by a study of 20 patients with positive test at concentration 0.1%, of whom only five reacted to patch tests with thiomersal at 0.01% (unfortunately, the authors did not mention whether those patients had thiomersal-related clinical symptoms) [69]. On the other hand, morphology and the 'crescendo' pattern of typical patch test reactions to thiomersal speak for an allergic rater than irritant (i.e., false-positive) reaction, which has left researches puzzled for half a century [70]. The case of thiomersal demonstrates difficulties with drawing undisputable conclusions from observations, which next to usual variations to epidemiological studies, were additionally biased by ongoing withdrawal of thiomersal-preserved vaccines and consumer products, and possibly also by a too high concentration of thiomersal used for routine patch testing.

Clinical trials of immunotherapy with haptens

The aforementioned animal and human experiments along with epidemiological observations seem to follow the scheme 'first tolerance induction, then attempts at sensitizing on the skin', which differs substantially from the typical real-life situation, where a patient seeks the cure only after having developed contact hypersensitivity. Interestingly enough, some researchers undertaking trials of hyposensitization seem not to have noticed this difference, as they point on the animal experiments as 'experimental basis' for their endeavors. As a matter of fact, most animal studies were on induction of tolerance in nonprimed animals, whereas in humans, all but one studies done so far were aimed at hyposensitization of people who were already found allergic. Basically, next to a few small studies dealing with various haptens (summarized in Table 1), there are two major episodes in the history of immunotherapy of ACD: one devoted to searching for cure for *Rhus* dermatitis, and a more recent one focused on desensitization of nickel allergy.

Table 1. Overview of studies on hyposensitization of people with allergic contact dermatitis caused by sensitizers other than *Rhus* and nickel.

Publication	Sensitizer	Route of administration	Formula and dosage	Study subject or group	Outcome measures	Results	Comments	Ref.
Constantine *et al.* (1975)	Mechlorethamine (nitrogen mustard)	Epicutaneous	Daily total-body applications of increasing concentrations of mechlorethamine, starting with extremely dilute solutions (0.01–0.1 mg/100 ml)	Five patients with MF who developed contact dermatitis to mechlorethamine	Symptoms	Three patients: desensitized during a period of 8–13 months to the point of tolerating the therapeutic concentration (20 mg/100 ml) One patient: unable to tolerate lowest concentrations One patient: remission of MF, no further need to continue desensitization	An open, uncontrolled trial in a small group of patients with malignant disease (possible interference with the immune response)	[101]
Pariser *et al.* (1976)	Mechlorethamine (nitrogen mustard)	Intravenous	Daily infusions of increasing doses, starting with 1 µg, increasing up to 200 µg per infusion (duration 6–8 h)	Eight psoriasis patients with ACD following topical application of mechlorethamine and positive patch test	Symptoms, reactions to open test, mechloretamine provocation	One patient: successful desensitization, relapse after 8 months Three patients: failure Two patients: withdrawal due to side effects Two patients: patch test-negative, severe pruritus after mechlorethamine provocation	An open, uncontrolled trial Objective outcome measures: skin tests, provocation	[102]
Fernandez de Corres *et al.* (1987)	*Frullania* plant	Epicutaneous	Fresh plant or extract	A farmer with multiple sensitization to plants	Symptoms	Fresh plant: Strong local reactions forcing discontinuation *Frullania* extract: no protection obtained	An uncontrolled, open trial in one person	[103]
Srinivas *et al.* (1988)	*Parthenium hysterophorus*	Oral	Dried, powdered *Parthenium* leaf, starting with 0.1 mg, increasing up to 1 mg	A patient with history of airborne dermatitis to *Parthenium*	Symptoms	Symptom-free after a few weeks, relapse within 10 days after discontinuation	An uncontrolled, open trial in one person	[104]
Handa *et al.* (2001)	*P. hysterophorus*	Oral	Ether extract of dried *Parthenium* leaves in corn oil, 5–30 drops of solutions of 10 mg/ml	24 patients patch test-positive to *P. hysterophorus*	Symptoms (clinical score), patch test titer	14 patients: a gradual fall in the score Six patients: exacerbation Four patients: drop off No change in patch test titer	An open, uncontrolled trial	[105]

ACD: Allergic contact dermatitis; MF: Mycosis fungoides.

Immunotherapy of *Rhus* dermatitis

More than a half of the US population are allergic to poison ivy and poison oak – plants from the genus *Rhus*, family *Anacardiaceae*, which include species widely distributed in the USA, known from their capacity to inducing severe contact dermatitis [49]. The first report claiming a successful desensitization in 11 out of 12 patients with *Rhus* dermatitis achieved by intramuscular injections of 'homologous vegetable toxins' was published by Strickler in 1918 [71]. Schamberg enthusiastically announced the 'uniform success' of subcutaneous and oral desensitization with *Rhus* extracts 1 year later [72], soon afterwards Bivings reported about a success rate of more than 98% [73]. These early studies were based on uncontrolled retrospective analyses and patients' testimonies. Four decades later, Kligman convincingly demonstrated that patient's satisfaction is not a reliable measure of therapeutic effectiveness: he administered injections of placebo (plain sesame oil) to 18 volunteers with severe poison ivy dermatitis: While the 'post-treatment' patch tests showed no objective decline in hypersensitivity, 16 of the subjects expressed high satisfaction with the treatment [49]. Back in the 1920s, Krause and Weidman fist employed patch tests for objective verification of the effectiveness of the procedure and reported on an aggravation rather than any decline of *Rhus* reactivity after the therapy [74]. In 1929, Templeton reported on further cases of adverse effects (disseminated urticaria and eczema) to this therapy [75]. Altogether, when looking at the overview of clinical studies on immunotherapy with *Rhus* extracts (collated in Table 2), it is hard to escape the impression that the poorer was the design of a trial (e.g., lack of placebo control and no objective outcome measures), the more the final conclusions were in favor of *Rhus* desensitization. Four decades after the first paper by Strickler, Kligman published results of his study of *Rhus* hyposensitization that spanned over a 3-year period and involved more than 2000 subjects. He meticulously measured their hypersensitivity by means of patch test with serial dilutions of PDC – purified hapten of *Rhus* oleoresin. In this most extensive ever study of hyposentizitation to haptens, Kligman tried out many different dosages, schedules and routes of administration, including intramuscular, intracutaneous, epicutaneous and oral. He found oral administration of PDC to indeed cause a definite decrease in *Rhus* hypersensitivity; however, this effect was only moderate and started to diminish a few weeks after discontinuing the treatment [46]. Due to abundance of data, Kligman's extensive paper, though 26 pages long, is rather a selective review of unpublished study results, than a detailed report of a therapeutic trial. That he did not publish all details of his studies is most unfortunate for future researchers, who are at risk of employing hyposensitization schemes that had been already proved ineffective. Nevertheless, although not the first one to demonstrate the limited effectiveness of *Rhus* immunotherapy, Kligman's study provided evidence strong enough to dare the following comment on the early reports "Therapeutic ambitiousness has colored the picture with extravagant claims". One of such studies of the effectiveness of tablets "for oral prophylaxis against poison ivy dermatitis that has established complete immunity in 95% cases" was critically reviewed by Hill [76]: After pointing out on major methodological errors in the study design, he finally concluded that a considerable number of those "…in whom 'protection' is claimed to have been conferred by the taking of the tablets would have been 'protected' if they had been treated by eating an owl's egg every morning for breakfast instead of taking the tablets". Undeterred by the growing body of evidence and criticism, marketing of products for parenteral and oral *Rhus* immunotherapy was continued in the USA for another 30 years until final withdrawal in late 1980s. Interestingly enough, *Rhus* extract is ingredient of homeopathic tablets that are still sold as a remedy against arthritis, also in countries with no occurrence of *Rhus*, which opens an opportunity for a new research on the oral induction of hapten tolerance.

Immunotherapy of nickel allergy

It is estimated that up to 65 million EU citizens may be allergic to nickel [31], with this hypersensitivity emerging already at young age [64]. The main clinical manifestation of nickel allergy is ACD, localized at the sites of skin contact to nickel. With regard of systemic allergy to nickel, a new entity 'systemic nickel allergy syndrome' was recently coined with the intention of embracing all types of adverse effects caused by oral ingestion of nickel, embracing systemic ACD to nickel, urticaria, but also gastrointestinal symptoms [77]. Orally ingested nickel is also accused as a major cause of generalized itch without any visible signs of skin disease, a clinical entity referred to as '*pruritus sine materia*' [78]; however, diseases consisting only

Table 2. Overview of major studies on hyposensitization of *Rhus*-allergic patients.

Publication	Route of administration	Formula and dosage	Study group	Outcome measures	Results	Comments	Ref.
Strickler (1918)	Intramuscular	Alcoholic extract of "sumac toxin", "ivy toxin", or "*Rhus* toxin", 1–4 occasional injections of 0.3–1.0 cm^3	12 patients with "dermatitis venenata" with positive reaction to intracutaneous test with *Rhus* extract	Clinical observation	8/12 "cured", "free of attacks" or "absolutely normal" 3/12 improvement 1/12 recurrence within 1 month	A collection of 12 case reports	[71]
Schamberg (1919)	Subcutaneous	Aqueous solution of *Rhus toxicodendron* alcoholic extract	"A score of susceptible persons"	Clinical observation	"All have remained free of dermatitis during the ivy season"	A retrospective report of clinical experience with a small case series	[72]
	Oral	Alcoholic extract of *Rhus toxicodendron* dissolved in juice, increasing doses	A 12-year-old girl with severe dermatitis venenata	Clinical observation	"She was rendered immune"	Uncontrolled clinical observation of a single case	
Bivings (1924)	Subcutaneous, oral	As with Strickler	105 boys and girls aged 10–20 years, exposed to poison oak and poison ivy	Clinical observation	2/105 "failures" 13/105 "requiring tincture alone, relief in 12 h" 35/105 "relief after one injection" 38/105 "relief after two injections"	Retrospective analysis of uncontrolled clinical observations in a medium-sized case series	[73]
Krause and Weidman (1925)	Intramuscular, oral	*Rhus* extract, four injections of 0.5–1 cm^3 at 1–2-day intervals, followed by oral administration	Seven men with *Rhus* dermatitis confirmed in patch test	Skin reaction to *Rhus* extract or bark	"All seven of our volunteers developed a furious dermatitis, which lasted as long as or longer than previous attacks"	Open study, treatment result verified by controlled provocation (patch test)	[74]
Molitch and Poliakoff (1936)	Subcutaneous	*Rhus* extract, weekly injections, 1 cm^3 dose of dilutions increasing from 1:10,000 to 1:500	40 boys aged 8–18 years with positive skin reaction to poison ivy extract	Clinical observation and history	"Not one of the subjects had ivy poisoning during the period of treatment"	Uncontrolled clinical observation of a small case series	[106]
Simon and Lotspeich (1939)	Intramuscular	Poison ivy extract	Eight sensitive patients	Patch tests at three different dilutions of poison ivy extract (1:100, 1:1000 and 1:10,000)	No change in specific reactivity of the skin	Uncontrolled, open study, treatment result verified by controlled provocation (patch test titer)	[107]
Zisserman and Birch (1939)	Intramuscular	*Rhus* extract	304 out of 1731 boy scouts	Incidence of subsequent poison ivy dermatitis	Incidence in the treated group: 51.6%, compared with the total incidence in the camp: 33.6% "The massive standard dose method of rapid prophylaxis for poison ivy dermatitis is not generally beneficial and actually makes many patients more susceptible. Its routine use is contraindicated"	Interventional observation, mixed study group – some subjects had a history of *Rhus* dermatitis, others did not	[108]

ACD: Allergic contact dermatitis; HDC: Heptadecylcatechol; PDC: Pentadecylcatechol.

Table 2. Overview of major studies on hyposensitization of *Rhus*-allergic patients.

Publication	Route of administration	Formula and dosage	Study group	Outcome measures	Results	Comments	Ref.
Greenberg and Mallozzi (1940)	Intramuscular	Two injections of 1 cm^3, *Rhus* extract (77 men) or blank vehicle (42 men) at 2-week intervals	119 men sensitive to *Rhus* extract	Patch test with a dilution series of *Rhus* extract, 6 weeks after second injection	"No significant reduction of the skin's sensitivity to poison ivy could be objectively demonstrated"	Well-designed, placebo-controlled study with a well-defined objective outcome measure	[109]
Shelmire (1941)	Oral	One ounce of a 1:25 or 1:10 dilution of poison ivy leaf or root oleoresin in corn oil, ingested during a period of several months	30 white individuals sensitive to poison ivy, aged 14–45 years	Patch test titer to poison ivy extract	Treated group: "varying degrees of reduction of cutaneous sensitivity followed ingestion of the specific oil". No reduction of the level of sensitivity of the skin occurred in untreated controls	Open, controlled trial, no placebo, with a well-defined objective outcome measure	[110]
Zisserman (1941)	Oral	Ether-soluble poison ivy extract 0.01 mg in enteric tablets, one tablet daily in the first week, followed by one tablet twice a week	Boys at a summer camp sensitive to poison ivy: 53 assigned to therapy group; 578 nontreated controls	Recurrence of poison ivy dermatitis	Recurrence rates: 52.8% among treated, 56.8% among untreated	Well-designed intervention study with control group, outcome measure sensitive to random variability	[111]
Kligman (1958)	Oral	Cashew nut shell oil 10% increasing from one to 20 drops daily dissolved in water and drunk through a straw. Duration of 8–10 months. Cumulative doses: 35 ml	43 *Rhus*-sensitive volunteers aged 5–62 years	Exposure to fresh poison ivy leaves	"Hyposensitization of *Rhus*-sensitive persons may be satisfactorily achieved by the graduated oral administration of 10% cashew nut shell oil in ethyl alcohol"	Open, uncontrolled trial. No exact numerical results are given. Cashew nut shell oil was tested as a possible cheap alternative to *Rhus* oleoresin	[112]
Epstein *et al.* (1974)	Oral	Urushiol in olive oil, increasing daily doses until a cumulative dose of more than 250 mg, followed by a maintenance phase of 1–2 mg for 5 days a week for up to 23 months	27 *Rhus*-sensitive volunteers, nine assigned to each of urushiol, placebo or no medication	Patch test titer to urushiol	Improvement found in: 6/9 urushiol treated, 1/9 placebo treated, 1/9 no treatment	Double-blind, placebo-controlled study	[113]
Epstein *et al.* (1982)	Oral	Capsules with urushiol oil gradually increasing doses up to 11.5 mg daily for 3–6 months (cumulative dose: over 300 mg)	Adults aged 20–51 years, history of *Rhus* dermatitis, highly sensitive to urushiol on patch testing, 21 assigned to treatment group (urushiol oil), 12 assigned to placebo group (corn oil)	Patch test titer to urushiol	Treatment group: decrease of patch test sensitivity in 15 out of 21; placebo group: decrease of patch test sensitivity in 2 out of 12 ($p < 0.01$)	Well-designed, double-blind, placebo-controlled trial with objective outcome measures	[114]
Marks *et al.* (1987)	Oral	1:1 mixture of PDC and HDC diacetate	87 patients with history of ACD to poison ivy (44 assigned to PDC/HCD treatment, 43 to placebo)	Patch test titer to urushiol	No significant difference between the PDC/HCD and placebo groups	Well-designed, placebo-controlled trial with randomization and objective outcome measures	[80]

ACD: Allergic contact dermatitis; HDC: Heptadecylcatechol; PDC: Pentadecylcatechol.

of subjective symptoms are difficult to study and scientific evidence for this alleged role of nickel seems limited [79]. Nickel, as a ubiquitous hapten is difficult to avoid, and present consumer protection laws seem not fully sufficient with this respect [55,56]. Therefore, a possibility of effective hyposensitization of people allergic to nickel would be of a great social and economical impact. In 1987, at the time of announcing rather discouraging results of the last trial of *Rhus* immunotherapy in the US [80], Sjovall *et al.* published in Europe results of the first double-blind, placebo-controlled trial of nickel hyposensitization: after oral administration of 5 mg Ni/week, they observed a decrease in patch test titers indicating on a reduced sensitization. However, some patients experienced aggravation of their dermatitis during the treatment [81]. Further studies of immunotherapy with nickel are collated in TABLE 3. Most of these are characterized by poor design (e.g., no placebo and no blinding) topped with triumphant claims about the treatment effectiveness. One of the major problems not yet solved seems the selection of nickel dose during oral immunotherapy: for example, hardly any authors state whether the administered dose (weight) pertains to pure nickel, nickel sulfate (in such case, nickel would amount to 38% of declared weight), or perhaps nickel sulfate hexahydrate – the form of nickel most commonly used in allergy diagnosis and research, in which nickel makes up only 22% of the total weight. Moreover, authors of two trials have tested as little as 1–2 ng of nickel, a 'homeopathic' dose that is far below the environmental background exposure. Such dose is roughly equivalent to a spoonful of tap water (compare also comments to TABLE 3), and yet the authors claim that they have seen clearance of symptoms or improvement in 59–64% of their patients [82,83]. On the opposite end of the range is a 5 mg dose used in two well-designed studies, of which one reported on positive outcome [81], while no clinical effect could be observed in the other [84]. It seems that this dose might indeed be effective biologically, as it is within the range of doses provoking systemic ACD: flare ups and generalizations of ACD have been reported at doses from 1.0 to 5.6 mg [85–87]. These adverse effects can be avoided by a stepwise increase of nickel doses, though this would not be effective in all patients. Santucci *et al.* exposed 25 nickel-allergic patients to a single oral dose of 10 mg $NiSO_4$ hydrate (2.2 mg pure Ni), which led to an aggravation of ACD in 18 individuals. When 17 patients from this group were re-exposed to repeated daily doses starting with 3 mg $NiSO_4$ (0.7 mg Ni) and increasing gradually over 3 months, 14 of them, but not all, could tolerate the previously offending dose of 10 mg $NiSO_4$. A relevant yet discouraging observation from Santucci's study was that although oral tolerance to ingested nickel had increased, hyposensitization of the skin was not achieved – patch test reactivity and jewelry intolerance remained unchanged [88]. One of the possible explanations might be that next to the specific, immunologically mediated hypersensitivity there seems to exist also an 'alternative pathway' for nickel intolerance: the 'classical pathway' requires specific lymphocytes to recognize via T-cell receptors the hapten–protein complexes presented to them within the MHC of APCs. The highly reactive molecules of nickel seem capable of bypassing this step of antigen recognition by 'zipping together' MHC molecules of random APCs with T-cell receptors of random lymphocytes, which would results in nonspecific lymphocyte activation resembling the effects of bacterial superantigens [89,90]. The frequently of people affected by this 'alternative pathway' among all nickel-sensitive patients is unknown; nevertheless, it seems least probable that they would profit from any form of immunotherapy. Putting all the above observations together, data published until now do not allow for any definite statement about the effectiveness of oral hyposensitization in nickel-allergic patients.

Conclusion

In the history of hapten immunotherapy research, much confusion seems to have resulted from mixing up two phenomena: prophylaxis (i.e., the prevention of future sensitization) and hyposensitization (i.e., decreasing existing hypersensitivity). Most of the successful animal experiments were focused on the first phenomenon, while second constituted the aim of most clinical trials. With few exceptions, the history of research of hapten hyposensitization may be viewed as an epic of two episodes: 'Episode One' was on *Rhus* hyposensitization – an adventure set in the USA that begun in 19th Century and concluded in 1987. In this very year, 'Episode Two' started – the nickel hyposensitization saga that is unfolding in front of our eyes right now, mainly in Europe. Sadly, most heroes of the 'Episode Two' seem unaware of what happened

Table 3. Overview of clinical trials of hyposensitization to nickel.

Publication	Route of administration	Formula and dosage	Study group	Outcome measures	Results	Comments	Ref.
Sjovall *et al.* (1987)	Oral	Nickel sulfate, two protocols: 5 mg oral (equivalent to 1.9 mg nickel)† once a week, or 0.5 mg daily (0.19 mg nickel)† for 6 weeks	24 patients with ACD to nickel for each protocol	Patch test score	Reduced patch test scores after oral exposure to 5 mg but not at 0.5 mg, exacerbations observed in some patients	Placebo-controlled trial, objective outcome measure	[81]
Panzani *et al.* (1995)	Oral	Nickel sulfate tablets 0.1 ng (equivalent to 0.038–0.076 ng nickel)†, 1–2 tablets per day for 2–3 years	51 patients with "dermatological allergy to nickel" (erythema, urticaria, angioedema or contact dermatitis)	Patient-reported symptoms, patch test outcome, oral provocation	30/51 clearance of symptoms or improvement; 7/51 relapse	Open trial, no placebo, no blinding; heterogeneous group of patients, high drop-off rate, declared content of nickel far average background oral exposure‡	[82]
Troost *et al.* (1995)	Subcutaneous	Nickel sulfate injections at increasing weekly doses up to 1 ml of a 10^{-3} mol/l solution (equivalent to 58.7 µg nickel/maximal dose)† for 2 years	12 patients with ACD to nickel treated with nickel and UVB, 9 patients treated with UVB only	Clinical score, patch test reaction, lymphocyte proliferation assay	"No statistically significant difference between the groups was seen"	Open trial, comparison of UVB therapy alone with UVB therapy and Nil immunotherapy	[115]
Morris (1998)	Sublingual	Nickel sulfate in glycerol/saline drops, starting dose established on intracutaneous tests, 3 times per day, gradually increasing up to 2.3 µg (equivalent to 0.87 µg nickel/maximal dose)†, the average duration of treatment was 16 months	39 patients with dermatitis and positive intracutaneous test with nickel	Mailed questionnaire, assessment of the effectiveness by patients	4/39 "unlimited tolerance", 9/39 "much better", 20/39 "noticeably better", 6/39 "unchanged"	Open trial, no placebo, no controls, no blinding, duration 16 months, declared content of Nil far below average background oral exposure‡	[116]
Bagot *et al.* (1999)	Oral	Nickel sulfate equivalent to 5 mg nickel in gelatin capsules, once a week over 7 weeks	30 patients with nickel contact eczema	Clinical examination (intensity of skin lesions, course), quantitative patch test, lymphocyte transformation	No effect on clinical symptoms and patch tests, reduction of the number of circulating nickel-specific lymphocytes in peripheral blood	Double-blind, placebo-controlled trial of a small group	[84]

†Own calculations based on data extracted from the article. Although not specifically mentioned in all but the last article, the most common form of nickel that was most probably used is the hexahydrate of nickel sulfate. In such cases, the calculated equivalents of pure nickel should be additionally divided by 1.73 in order to determine the real doses of nickel.
‡Nickel content in one glass of tap water ranges from 40 to >800 ng [119–121]*, while average dietary uptake of nickel ranges from 150,000 to 900,000 ng/day* [122].
§The authors diagnosed SNAS in patients with history of ACD to nickel combined with cutaneous (urticaria or eczema developing in areas not exposed to immediate contact with nickel) and gastrointestinal symptoms (nausea, dyspepsia, heartburn, meteorism, abdominal pain, diarrhea or constipation) and/or respiratory symptoms with beneficial effects of a nickel-free diet, a positive patch test to nickel and positivity of a double-blind placebo-controlled oral nickel challenge [77,123].
ACD: Allergic contact dermatitis; PBMC: Peripheral blood mononuclear cell; SNAS: Systemic nickel allergy syndrome.

Table 3. Overview of clinical trials of hyposensitization to nickel.

Publication	Route of administration	Formula and dosage	Study group	Outcome measures	Results	Comments	Ref.
Schiavino *et al.* (2006)	Oral	Nickel sulfate, 1–2 granules each of 0.1 ng (equivalent to 0.038–0.076 ng nickel)† daily for 10 months	Patients with contact allergy to nickel with history of cutaneous and/or digestive symptoms, prick or patch test positive; 136 assigned to treatment, 95 controls instructed to keep low-nickel diet	Clinical follow-up for 6 months, oral challenge, patch tests	Treatment group: 47% "complete remission", 17% "improvement over 80%", 5% "partial benefit", 31% dropped out due to lack of effectiveness, Control group: 82% relapse	Open trial, no placebo for controls, no blinding Heterogeneous group of patients (e.g., ACD and gastrointestinal symptoms), high drop-off rate, Nil content in the granules far below average background oral exposure‡	[83]
Tammaro *et al.* (2009)	Oral	Nickel sulfate granules, incremental doses 0.1 ng–1 µg (equivalent to 0.038–380 ng nickel)† every second day or every day for 1 year	122 patients with SNAS§: 67 assigned to hyposensitization, and 55 controls receiving no treatment	Clinical follow-up after 1, 3, 6 and 12 months	Treatment group: 100% "significant benefit" after 4 weeks of treatment (daily dose at this stage: 1 ng nickel sulfate); 27% adverse effects (dermatitis, itch or indigestion) Control group: no mention	Open trial, no placebo for controls, no blinding, no results for control group Very specific inclusion criteria (SNAS) that seem representative of a relatively small fraction of nickel-allergic patients	[117]
Minelli (2010)	Oral	Nickel sulfate hexahydrate ($NiSO_4 \times 6H_2O$) in hard gelatin capsules, incremental phase of nickel (from 0.1 ng to 3 µg, equivalent to 0.022–0.66 µg nickel/dose)† three times per week, followed by a 12-month maintenance (1.5 g/week)	36 patients with SNAS§: 24 assigned to hyposensitization + low-Nil diet, and 12 controls receiving the diet only	Symptom diary, visual analog scale, IL-5, symptoms after reintroduction of nickel-rich food, IL-13 and IFN-γ secretion of PBMCs in response to nickel	1/24 drop off (due to gastrointestinal symptoms in the incremental phase), After reintroducing nickel-rich food: Treated group: 20/24: symptom free, 3/24: relapse, Controls: 12/12 relapse No differences in cytokine secretion by PBMCs	Open trial, no placebo for controls, no blinding Very specific inclusion criteria (SNAS) that seem representative of a relatively small fraction of nickel-allergic patients	[118]

†*Own calculations based on data extracted from the article. Although not specifically mentioned in all but the last article, the most common form of nickel that was most probably used is the hexahydrate of nickel sulfate. In such cases, the calculated equivalents of pure nickel should be additionally divided by 1.73 in order to determine the real doses of nickel.*

‡*Nickel content in one glass of tap water ranges from 40 to >800 ng* [119–121]*, while average dietary uptake of nickel ranges from 150,000 to 900,000 ng/day* [122].

§*The authors diagnosed SNAS in patients with history of ACD to nickel combined with cutaneous (urticaria or eczema developing in areas not exposed to immediate contact with nickel) and gastrointestinal symptoms (nausea, dyspepsia, heartburn, meteorism, abdominal pain, diarrhea or constipation) and/or respiratory symptoms with beneficial effects of a nickel-free diet, a positive patch test to nickel and positivity of a double-blind placebo-controlled oral nickel challenge* [77,123].

ACD: Allergic contact dermatitis; PBMC: Peripheral blood mononuclear cell; SNAS: Systemic nickel allergy syndrome.

in 'Episode One'. History went full circle, or perhaps is there still a chance that we learn from previous mistakes?

Future perspective

Experiments with human subjects have demonstrated that some people remain tolerant to urushiol or nickel in spite of repeated attempts at sensitizing them [91–93]. Although human studies are nowadays much more difficult to perform, a deeper look into the problem with the help of modern research methods might provide a break-through in this area. White *et al.* suggested that induction of oral tolerance might be an everyday situation, and early oral exposure to haptens could determine a person's future allergic career [94], a hypothesis that certainly deserves due attention. With this respect, relevant data may be acquired from well-designed studies of populations living in areas with high levels of certain haptens in the environment (e.g., nickel [95]). Furthermore, clinical and epidemiological experience shows that not all people with detectable contact allergy (understood as positive patch test results) will develop any clinical symptoms when exposed to the hapten. This is referred to as clinical relevance: a patch test result is relevant when patient's exposure to this hapten causes clinical symptoms; when the patient has no symptoms to the hapten, such result is deemed clinically nonrelevant. Such cases might be explained by false-positive (irritant) test reactions, misinterpretation of environmental exposures, but also by acquired immune tolerance, which seems most interesting with respect to the topic of this article. There is less positivity in patch test among children (13–24%) [96] than adults (26–40%) [97,98], however, the rate of clinically relevant patch test reactions is highest in youngest age groups: Goncalo *et al.* found the highest rate of relevant patch test reactions (94.4%) among children aged up to 5 years as compared to older children (68.3–77.5%) [99]. In another words, with increasing age there are more cases of hypersensitivity (positive patch test) without clinical symptoms, which among other possible causes may reflect acquisition of tolerance. Studies dedicated to this phenomenon might lead to discoveries relevant to the topic of hapten hyposensitization.

Generating *ex vivo* human T-cell suppressor subsets specific to urushiol as demonstrated by Kalish and Wood seemed promising also in context of other haptens, unfortunately, this line of research was discontinued and the latest report dates 1997 [100]. Dedicated studies of aforementioned phenomena might provide better understanding on how to restore immune tolerance to haptens in people with ACD. Nevertheless, the most urgent need of today is an independent, multicenter study of oral hyposensitization to nickel in a large population of patients with well-defined inclusion criteria and objective outcome measures of the therapy. Such study protocol should be carefully designed, based on the experience and evidence collected by outstanding researchers over the last century. Without results from such well-designed objective studies, we will still remain halfway between science and science fiction.

Executive summary

- Allergic contact dermatitis (synonym: allergic contact eczema) is inflammatory skin disease that develops in a person hypersensitive to a low-molecular-weight chemical (hapten), following cutaneous exposure to this hapten.
- Immunotherapy of allergic contact dermatitis is aimed at inducing unresponsiveness to haptens through induction of immune tolerance to prevent sensitization, or hyposensitization to reduce existing hypersensitivity to a hapten.
- Animal studies have demonstrated that extracutaneous (e.g., oral, intraperitoneal or intramuscular) administration of a hapten decrease the possibility of inducing hypersensitivity through skin exposure.
- The circumstances of animal experiments (tolerance induction before attempted sensitization) substantially differ from the situation of patients with delayed-type contact hypersensitivity (need for a cure of already existing hypersensitivity).
- In the field of clinical research, there are too many poorly designed uncontrolled therapeutic trials with overoptimistic claims about the alleged therapeutic successes.
- Contact allergy to poison ivy and poison oak represents a major burden to public health and economy in the USA. After several decades of use, immunotherapy with *Rhus* vaccines and tablets was finally deemed as ineffective and discontinued in the 1980s.
- Nickel allergy is a worldwide problem comparable with that of *Rhus* dermatitis in the USA. Trials of hyposensitization to nickel were undertaken in late 1980s. At this stage, methodological flaws of most of these studies do not allow for any conclusion about the effectiveness of nickel immunotherapy.
- There are real-life situations that provide insight into prophylactic effect of oral hapten exposure, including differences between people exposed to urushiol via oral route (e.g., Israel and Hawaii) or the skin (USA), nickel-releasing jewelry versus nickel-releasing orthodontic appliances, and intramuscular vaccines preserved with thiomersal versus thiomersal-preserved cosmetics.
- Further studies are needed, including studies of the natural development of tolerance to haptens with increasing age, and most of all, well-designed multicenter trials on nickel hyposensitization.

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