Contact Urticaria Syndrome

Edited by

Ana M. Giménez-Arnau ▪ Howard I. Maibach

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We hope that this textbook can be useful for you in your routine professional tasks. We encourage you to work in this field, promoting an increase of knowledge especially about the unmet needs. Just a common approach through the clinical expression of the syndrome, the diagnostic tools, and the contact triggers involved will help to answer the questions that we have regarding epidemiological, mechanistic, or prognosis aspects. We, as editors, welcome comments or suggestions for the next edition.

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Preface

It has been nearly four decades since contact urticaria syndrome was described for the first time (Maibach and Johnson, *Archives of Dermatology* 1975; 111:726–730). At that time diethytoluamide was responsible for an immediate type of hypersensitivity reaction characterized by contact-induced wheals. Since then, immediate skin contact reactions, pruritus, dermatitis, or urticaria were described as induced by multiple contact triggers. The increasing interest in this field was the reason for the book *Contact Urticaria Syndrome*, edited by Amim and Maibach in 1997. This text showed what was known at that time and summarized the experience of clinical investigators worldwide.

Since then, our knowledge about the contact urticaria syndrome has increased, especially during the epidemic of contact urticaria induced by latex. Through isolated or short series of reported cases, we've learned that proteins, but also low-molecular-weight substances, are capable of inducing the signs and symptoms. And, obviously slowly, the approach to the pathogenesis and the individual behavior of each trigger helps to better understand why these immediate contact reactions can be expressed through different clinical patterns. This updated book about contact urticaria syndrome extends previous experience.

But even now, in the twenty-first century, immediate cutaneous skin reactions such as pruritus, eczema, or wheals are underdiagnosed. Still dermatologists, allergologists, and occupational physicians rarely make the immediate diagnosis of contact skin reactions. Habitually, the simple question, "When did your symptoms start?" or "What was the interval between the contact and the symptom appearance?" is missing. Hopefully, the clinical experience summarized here will lead to a more accurate diagnostic approach. The appropriate diagnostic tool can be selected just by using a detailed history. And the appropriate diagnosis will lead to a better preventive and therapeutic approach. This is obviously important whenever a disease has a demonstrated impact in the quality of life and occupational relevance.

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Contact Urticaria Syndrome: Definition, History, Etiology, and Relevance

Ana M. Giménez-Arnau and Howard I. Maibach

Skin is the target organ of environmental agents. Through epidermal and dermal homeostasis, the cutaneous tegument has the main task of preserving our life. At least five fundamental skin roles can be defined: mechanical barrier function, melanogenesis, immunological barrier function, thermoregulation, and environmental perception. The epidermal and dermal binomiun is by itself a complex and complete immunological organ. The epidermal presence of specific specialized antigen-presenting cells, the Langerhans cells as well as local lymphocytes, join with the dermal presence of pluripotential cells, as mast cells, making the skin an immunologically very active organ. Skin is vital.

The concept of contact dermatitis includes any inflammatory skin reaction to direct or indirect contact with noxious agents in the environment. Although the main clinical expression of contact dermatitis is eczema, others as urticaria, contact urticaria, or lichenoid eruptions, are described. Contact dermatitis was recognized as a disease in ancient times. The earliest recorded reports include Pliny the Younger who, in the first century A.D., noticed individuals with severe itching when cutting pine trees. The history of contact dermatitis in the twentieth century is indistinguishable from the history of patch testing, which is considered the main tool for discovering the etiology is a chemical or a protein as the responsible agent.

The main objective of this book is to explain, from different perspectives, a special type of contact dermatitis that often is misdiagnosed: contact urticaria syndrome (CUS). It is misdiagnosed because traditionally type I (immunoglobulin E [IgE] immediate) and type IV (lymphocyte delayed) cutaneous reactions were identified with specific clinical expressions: immediate wheals for type I and delayed eczema for type IV. Even the available diagnostic tools used for etiological study of these patients are traditionally different for the suspected type I or type IV reactions. During the past decades, we've learned that proteins and low-molecular-weight molecules can induce immediate cutaneous reactions clinically expressed with pruritus, wheals, and eczema through an immunological pathway that still necessitates being completely understood.

Definition and History of the Birth of CUS

CUS comprises a heterogeneous group of immediate contact inflammatory reactions that usually appear within minutes after contact with eliciting substances. Occasionally, systemic involvement can be present. It was defined as an entity in 1975 by Maibach and Johnson.[1] Since then, its scientific interest has increased and new cases are continuously reported, providing information concerning new trigger factors and clinical features.

Contact urticaria (CoU) refers to a wheal and flare reaction following external contact with a substance; it usually appears within 30 minutes and clears completely within hours without residual signs.[2] The term was introduced by Fisher (1973), but this phenomenon has long been recognized.[3] Urticarial lesions to nettles and hairy caterpillars were reported in the nineteenth century and continue being reported today.[4] In a randomly designed survey carried out in 1224 adults in Spain, contact wheals and pruritus were noticed by the 52.1% and 100%, respectively, of people who suffered cutaneous symptoms induced by pine processionary.[5] Furthermore, some naturally existing urticariogens were used therapeutically as rubefacients, counterirritants, and vesicants.[6]

Hjorth and Roed-Petersen defined (1976) protein contact dermatitis (PCD) as characterizing an immediate dermatitis induced after contact with proteins.[7–9] Thirty-three food caterers suffered exacerbation of an itch immediately after contact with meat, fish, and vegetables, which was followed by erythema and vesicles. Application of the relevant foods to the affected skin resulted in either urticaria or eczema.[10] Atopy and PCD are associated in approximately 50% of affected patients.[11]

Patients suffering CUS can develop CoU and/or dermatitis/eczema immediately after contact with the trigger substance. These immediate contact reactions can appear on normal or eczematous skin. Wheals are the characteristic symptoms in CoU. Eczema appears rapidly on the hands in PCD. Both cutaneous symptoms and entities can be induced by the same trigger factor and can be suffered by the same patient.

CUS, CoU, and PCD are conditions characterized by the immediate development of contact skin reactions (immediate contact skin reactions) mainly consisting of pruritus, wheals, and/or eczema.

CUS as Occupational Dermatosis: History and Unmet Needs

The global incidence of CUS is not known, but immediate contact reactions are common in dermatological practice.[12–17] With the exception of latex allergy showing prevalence of 5%–10%, the rest of the trigger factors are just isolated cases or describe a small series of patients.[18] In the occupational setting, CUS seems to be common, although a precise statistical analysis is difficult to obtain in most of the countries because of underreport.[19] In a few countries, CoU has been classified as a separate occupational skin disease. This has been the case in Finland since 1989. The Finnish Register of Occupational Diseases (1990–1994) showed that CoU was the second most frequent cause of occupational dermatosis (29.5%) after contact allergic dermatitis (70.5%).[20,21] The trigger agents were cow dander (44.4%), natural rubber latex (23.7%), and flour, grains, or feed (11.3%).[21] A lower proportion of occupational CoU was found in a retrospective study done in a tertiary-level clinic specializing in occupational dermatology in Melbourne, Australia, which showed an 8.3% CoU prevalence.[22] Hands, arms, and face were the most frequent body areas involved. Atopy was a significant risk factor for natural rubber latex, foodstuffs, or ammonium persulfate CoU. Health workers, food handlers, and hairdressers were the most common occupations affected. More recently, in a survey conducted in 335 restaurants, catering and fast-food employees in Singapore showed as more commonly having occupational dermatosis irritant contact dermatitis (10%), with occupational CoU urticaria sporadically reported just in two patients caused by lobster and prawn.[23] The nature of the exposure will probably determine the percentage of CoU risk.

Health care workers in Europe show a known prevalence of occupational CoU from 5% to 10%, whereas in the general population, it lies between 1% and 3%. Other occupations shows also a high risk for developing CoU because there are food handlers or people involved in agriculture, farming, floriculture, plastics, pharmaceutical and other laboratories, and hunters, veterinarians, biologists, or hairdressers. Atopy favors further sensitization where protein allergens are concerned.[24]

The classification of occupational dermatosis of the International Code of Diseases-11 includes contact dermatitis jointly with contact urticaria. Occupational screening questionnaires including specific questions searching for urticaria symptoms are very few. The long version of the Nordic Occupational Skin Questionnaire is one of them, including nine questions about urticaria symptoms.[25] A standardized method to evaluate the occupational relevance of CoU, such as that already developed for occupational contact dermatitis with Mathias' criteria [26], would be desirable.

Evolving Knowledge about the Mechanisms Involved in CUS

The mechanisms underlying immediate contact skin reactions are partially understood. Each trigger substance has its own mechanism or mechanisms of action.

Nonimmunologic contact urticaria (NICoU) is due to vasogenic mediators without involvement of immunological processes. Urticariogens may act following different patterns. The most classic example concerns dimethylsulfoxide, which damages the blood vessels, making them leaky and inducing mast cell degranulation.[27] Antihistamines do not inhibit reactions to DMSO and other NICoU-responsible agents, but acetylsalicylic acid and nonsteroidal anti-inflammatory drugs do (both orally and topically); therefore, a role for prostaglandins has been suggested.[28–30] Release of prostaglandin D2 without concomitant histamine release has been demonstrated following topical application of sorbic acid and benzoic acid.[31,32] Capsaicin pretreatment (which depletes substance P) does not impair NICoU, but does inhibit the allergen prick test flare of immunologic CoU (ICoU).[33] Nonspecific tachyphylaxis of variable duration has been associated with various urticariogens.[34] Sharp hairs from animals or spines from plants penetrating the skin can deliver a cocktail of irritant chemicals or pro-inflammatory mediators causing NICoU.[35]

The pathogenesis of ICoU reflects a type I hypersensitivity reaction, mediated by allergen-specific IgE in a previously sensitized individual.[36] Skin challenge involves allergen penetration through the epidermis, IgE binding on mast cells, its degranulation, and subsequent release of histamine and other vasoactive substances as prostaglandins, leukotrienes, and kinins.

Oral Allergy Syndrome (OAS) is generally the result of an IgE-mediated type I allergic response. People with birch pollinosis show cross-reactivity because its structural homology with Rosaceae fruits such as apples or peaches.[37–39] Nevertheless, some other foods such as peanuts (Ara h1 and 2) or fruits can induce OAS independently of pollinosis.

A combination of type I and type IV allergic skin reactions, the latter supported by positive delayed patch tests, has been suggested as PCD pathogenesis.[40,41] It has been speculated that PCD is an eczematous IgE-mediated reaction through proteins. PCD shows a similar reaction pattern to aeroallergen-induced atopic eczema or dermatitis.[42]

Demonstrated Responsible Agents of CUS

Proteins (molecular weight 10,000 to several hundred thousand) and chemicals (molecular weights below 1,000) can trigger CUS.[43]

Plant or animal proteins, chemicals such as drugs and preservatives, or more diverse substances such as metals and industrial chemicals can induce ICoU. Raw fruits and vegetables are a common cause of ICoU in daily life. Natural rubber latex allergy focused global interest in ICoU at the end of the twentieth century. Latex sensitization risk factors include atopy and prolonged exposure via damaged epidermis (e.g., glove wearers with hand eczema). Low-molecular-weight molecules normally act as haptens; nevertheless, for some of them IgE antibodies have been also demonstrated as, for example, sensitized workers reactive to platinum and nickel–serum albumin complexes.[44,45]

NICoU is defined by stinging nettle wheals induced from *Urtica dioica*. Other responsible agents are preservatives, fragrances, and flavorings in cosmetics, toiletries, topical medications, or foodstuffs such as benzoic and sorbic acid.[46] Household, industrial, insecticide, and laboratory chemicals can also induce NICoU.

Few substances elicit mixed features of NICoU and ICoU through an unestablished mechanism other than IgE, which is involved in ammonium persulfate-induced CoU, where specific IgG and IgM activate the complement cascade through the classical pathway.[47–49] Immediate reactions to formaldehyde do seem to be mediated by IgE, with a prostaglandin role suspected because of thromboxane B_2 and prostaglandin PGF_2 increased levels.[50,51]

A huge number of compounds can be responsible of occupational and nonoccupational CUS, including animal products, plants and plant derivatives, foods, fragrances, cosmetics, flavorings, medications, preservatives, disinfectants, enzymes, metals, and miscellanea of different substances. Tables 1.1 through 1.6 include most of the compounds that have been registered in the literature.[52–129]

TABLE 1.1

Animals, Plants, and Derivatives (Natural Products) Responsible for Immediate Contact Reaction

Animals and their derivatives

- Ammiotic fluid[a,b]
- Anisakis simplex
- Blood[a,b]
- *Brucella abortus*[b]
- Calf[a]
- Cow[a]
- Caterpillars[c]
- Cephalopodos (*Loligo vulgaris*)[a]
- Chironomus[b]
- Cockroaches[a,b]
- Corals[c]
- Dander[a,b]
- Dogs; milk, seminal fluid[a]
- Gut (pig)[a,b]
- Guinea pig[a,b]
- Hair (rat, mice)[a,b]
- Horse
- Human hair
- Jellyfish[b,c]
- Liver (mouse)[a]
- Locust Tee[a,b]
- *Lumbrineris impatiens*
- Mites[a,b]
- Moths[c]
- *Nereis diversicolor*
- Pig[a]
- Pearl oysters[a]
- Placenta (cow)[a,b]
- Saliva[b]
- Sarcophaga carnaria
- Rat[a]
- Roe deer
- Seminal fluidb
- Serum (amphibian)[a,b]
- Silk[b]
- Spider mite[a,b]
- Urine (mice, rat)[a,b]
- Worms[a]

Plants and derivatives

- Algae[b]
- Aloe (Morrow)
- Arugula[b]
- Birch[b]
- Bougainvillea
- Camomile[a]
- Camomlilla
- *Cannabis sativa*[a]
- Chrysanthemum[a,b]
- Cinchona[a]
- Coral[c]
- Corn powder
- Cotoneaster
- Crateagus (hawthorn)[b]
- Elm tree
- *Eruca sativa*[b]
- Eucalyptus[b]
- *Ficus benjamina*[b]
- Gerbera[a]
- *Grevillea juniperina*[c]
- *Hakea suaveolens*
- Larch
- Lichens
- Lilies[a,b]
- Lime (Tilia)
- *Limonium tartaricum*[a,b]
- Mahogany[a]
- Mulberry
- Obeche[a,b]
- *Phaseolus multiflorus*
- Parsley[b]
- Poppy flowers[b]
- Sea anemone[c]
- *Semecarpus anacardium*
- Sesame seeds[b]
- Sunflower seeds[b]
- Teak[b]
- Tobacco[a,b]
- Tropical woods[a,b]?
- Tulips[a,b]
- Verbena[a,b]

Plants derivatives

- Abietic acid
- Colophony[a,b]
- Cornstarch[a,b]
- Latex rubber[a,b]
- Turpentine[c]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.

[a] Occupational.

[b] Immunologic.

[c] Nonimmunologic.

TABLE 1.2

Foods and Food Additives Responsible for Immediate Contact Reaction

Meat[b]

- Beef[a]
- Calf[a,b]
- Chicken[a]
- Codfish
- Ham (*Tyrophagus putrescentiae*)
- Lamb
- Liver
- Pork[a]
- Sausage
- Turkey

Fish[a,b,c]

- Cod[a]
- Crab
- Frog[a,b]
- Herring[a]
- Lobster[a]
- Lupin
- Oysters[a]
- Plaice[a]
- Pork[a]
- Raw fish[a]
- Seafood[b]
- Shrimp[a]

Other animal products

- Cheese[a]
- Eggs[a]
- Honey
- Milk[a]

Fruits[b]

- Almond[a]
- Apple[a]
- Apricot
- Apricot stone[a]
- Banan[a]
- Kiwi
- Litchi
- Lemon[a]
- Lemon peel[a]
- Lime[a]
- Mango
- Nuts[b]
- Orange
- Peach
- Peanuts
- Peanut butter
- Plum
- Strawberry[a]
- Watermelon[a]

Seeds[b]

- Sesame seeds[b]
- Sunflower seeds[b]

Grains[b]

- Buckwheat[a]
- Flour[a]
- Maize[a]
- Malt
- Rice[a]
- Wheat[a]
- Wheat bran

Vegetables[b]

- Asparagus[a,b]
- Arugula[b]
- Beans[a]
- Cabbage[a,b]
- Carrots[a]
- Castor bean[a,b]
- Celery[a]
- Chamomilla
- Chicori
- Chives
- Coffee been (green)[a,b]
- Cucumber pickle[a,b]?
- Dill[b]
- Endive[a,b]
- Fungi
- Garlic[a,b]
- Lettuce[a,b]
- Lime[a]
- Mentha[a]
- Mushrooms[a,b]
- Mustard[a,b]
- Onion[a,b]
- Parsley[a]
- Parsnip[a]
- Potato[a]
- Rice[7]
- Rocket
- Runner bean[c]
- Rutabaga (Swede)
- Salami casing molds[a,b]

TABLE 1.2 (*Continued*)

Foods and Food Additives Responsible for Immediate Contact Reaction

- Soybean[a]
- Stock (Matthiola incana)
- Tomato[a,b,c]
- Winged bean[a,b]

Flavoring and fragrances

- Balsam of Peru[b,c]
- Benzaldehyde[a,c]
- Benzoic acid
- Cinnamon oil
- Cinnamic acid[c]
- Cinnamic aldehyde[a,c]
- Gum arabic[a,b]
- Menthol[c]
- Vanillin[c]

Condiments and spices

- Cayenne pepper[c]
- Caraway[a]
- Coriander
- Curry[a]
- Paprika (*Capsicum annuum*)[a,b]
- Thyme[c]

Coloring agents

- Amaranth
- Allura red
- Cochineal red
- Ponceau
- Sunset yellow
- Tartrazine

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.3

Fragrances and Cosmetics Responsible for Immediate Contact Reaction

Hair care products

- Ammonium persulfate[a]
- Basic blue 99 (amino ketone dye)[b]
- Henna[a,b]
- Panthenol
- Protein hydrolysate[a]
- Paraphenylenediamine[a,b]

Emulsifiers

- Cetyl alcohol
- Polysorbate
- Sorbitan monolaurate
- Sorbitan monostearate
- Sorbitan sesquiolate
- Stearyl alcohol

Fragrances

- α-Amyl cinnamic aldehyde[c]
- Anysil alcohol[c]
- Balsam of Peru[a,b,c]?
- Cassia oil[c]
- Carvone[b]
- Cinnamic aldehyde[c]
- Cinnamic alcohol[c]
- Cinnamic acid[c]
- Coumarin[c]
- Eugenol[c]
- Geraniol[c]
- Hydroxycitronellal[c]

Other substances

- Allantoin
- Aloe gel[b]?
- Benzophenone[b,c]
- Colophony[b]
- Chamomile extract[b]?
- Chestnut peel[b]
- Elastin, fish-derived[b]
- Glycolic acid peel[b]
- Lecithin[b]?
- Melissa extract[b]?
- Pyrrolidone carboxylate[c]
- Propylene glycol[c]
- Resorcinol[c]
- Wheata,[b]
- Wool alcohol[b]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.4

Drugs Responsible for Immediate Contact Reaction

- Acetylsalicylic acid
- Aescin[b]?
- Aminophenazone
- Ampicillin[b]
- Amoxicilin[a]
- Bacitracin[b]
- Benzocaine
- Benzoyl peroxide[b]
- Capsaicin[c]
- Carboxymethylcellulose sodium[b]
- Chloroform[c]
- Cephalosporins[a,b]
- Cisplatin[a,b]
- Chloramphenicol[b]
- Chlorpromazine
- Dinitrochlorobenzene
- Diphenylcyclopropenone[b]
- Dimethylsulfoxide[c]
- Donezepil
- Gentamycin[b]
- Guanidinium salts[a]
- Hexylene Glycol[b] (excipient)
- Iodochlorhydroxyquin[b]
- Ketoprofen
- Lidocaine
- Levofloxacine[b]
- Levopromazine[a]
- Lindane[b]
- Mechlorethamine[b]
- Methamizole[a]
- Mezlocillin[a,b]
- Neomycin[b]
- Nicotinic acid esters[c]
- *N,N*-diethyl-meta-toluamide (DEET)[b]
- Penicillin[a,b]
- Pentamidine isethionate[a,b]
- Phenothiazides[b]
- Pilocarpine
- Prophylphenazone
- Promethazine
- Pyrazolones[b]
- Rifamycin[b]
- Sodium fusidate[b]
- Steroids
- Streptomycin[a,b]
- Tar extracts[c]
- Tincture of benzoin[c]
- Uranium salts[a]
- Virginiamycin[b]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.5

Preservatives Responsible for Immediate Contact Reaction

- Acetic acid
- Aescin polysulfate
- Alcohols[b,c]
  - Amyl
  - Ethyl
  - Butyl
  - Isopropyl
  - Benzyl[b,c]
- Ammonia[b]
- Benzoic acid[b,c]?
- Benzyl alcohol
- Bronoprol[c]
- Butilated hydroxytoluene[b]?
- Camphor[c]
- Chloramine[b]
- Chlorhexidine[b]
- Chlorine
- Chlorocresol[a,b,c]
- Formaldehyde[a,b,c]
- Gentian violet[b]
- Hexylene glycol[b]
- Imidazolidinyl urea[c]
- Kathon CG[c]
- Mercurochrome[b]
- α-phenylphenate[b]
- P-chlorocresol
- Parabens[b]?
- 2-phenoxyethanol
- Phenylmercuric acetate[a,b]
- Phenyl mercuric propionate[b]
- Polyethileneglycol
- Sodium benzoate[a,c]
- Sodium hypochlorite[b]
- Sorbic acid[c]
- Triclosan[b]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.6

Miscellaneous Chemicals and Metals Responsible for Immediate Contact Reaction

- Acetyl acetone[b]
- Acid anhydrides[a,b]
- Acrylic acid[b]?
- Acrylic monomers[a,b]
- Aliphatic polyamide[a,b]
- P-aminodiphenylamine[a,b]
- Aminothiazole
- Aziridine[a,b]
- Benzonitrile[a]
- Butylhidroxytoluol
- Calcium hypochloride
- Carbamates[a,b]
- Carbonless copy paper[a,b]
- Chlorotalonil[a,b]
- Citraconin anhydride
- Denatonium benzoate[a,b]?
- Di(2-ethyhexyl)phthalate[a]
- Dicyanidiamide
- Didecyl dimethyl ammonium chloride[a,b]
- Diethylfumarate
- Diethyltoluamine[b]
- Dimethyl ammonium chloride[a]
- Didecyl dimethyl ammonium chloride
- Diclycidyl ether of bisphenol A[a,b]
- Formaldehyde resin[a,b]
- Fumaric acid
- Guanidinium salts[a]
- Methyl ethyl ketone[b]
- Monoamylamine[b]
- Naphta[a,c]
- Naphthylacetic acid
- Nitrile[a]
- Nylon[b]
- Oleylamide
- Phosphorus sesquisulfide
- Polypropylene[a]
- Potassium ferricyanide
- Sodium fluoride
- Sodium silicate
- Sodium sulfide
- Sulfur[c]
- Triphenyl phosphate[a]
- Trichloroethanol
- Uranium salts[a]
- Vinyl pyridine[a]
- Xylene[a]
- Zinc diethyldiothiocarbamate[a]
- Metals
  - Aluminum
  - Chromium[a,b]
  - Cobalt[a,b]
  - Copper
  - Gold
  - Iridium[a,b]
  - Mercury[b]?
  - Nickel[a,b]
  - Palladium
  - Platinum salts[a,b]
  - Rhodium[a]
  - Ruthenium
  - Tin
  - Zin[c]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

Looking for Answers to Challenges Afforded in This Second Edition of CUS

Until now, we assumed new cases of CoU, PCD, or CUS as exceptional findings, adding new triggers each year to long lists of substances. But is this condition really exceptional? General population-based epidemiological studies are still lacking. Proteins and low-molecular-weight chemicals can be responsible for clinical manifestations, urticaria, or eczema, which are a consequence of different pathogenic mechanisms. Are the intrinsic properties of the environmental trigger of CUS responsible for the specific immunological pathway involved? Sometimes the same substance can induce both clinical patterns. This fact opens the door for new insights into new immune

system pathways. Substances responsible for immediate contact skin reactions can be classified by molecular weight, mechanism of action, occupational relevance, or their common use in our daily life. Our diagnostic tools still are based in subjective assessment. How can we improve these tools? It will be useful to replace *in vivo* tests with effective *in vitro* testing for diagnostic purposes. How do we better understand the disease behavior to help us develop effective preventive measures? A correct etiological diagnosis is necessary. After the symptoms, controlling the development of concrete preventive measures is required. After reading this book, we will most likely conclude that CUS is a worldwide health problem that needs a global approach.

REFERENCES

1. Maibach HI, Johnson HL. Contact urticaria syndrome: Contact urticaria to diethyltoluamide (immediate type hypersensitivity). *Arch Dermatol.* 1975;111:726–730.
2. Wakelin SH. Contact urticaria. *Clin Exp Dermatol.* 2001;26:132–136.
3. Fisher AA. Contact dermatitis.2nd ed. Philadelphia: Lea & Febiger, 1973; p. 283–286.
4. Lesser E. *Lehrbuch der Haut-und Teschlechtskrankheiten fur studirende und arzte* (in German). Leipzig: Verlag von FCW Vogel, 1894.
5. Vega JM, Moneo I, Garcia Ortiz JC et al. Prevalence of cutaneous reactions to pine processionary moth (Thaumetopoea pityocamba) in an adult population. *Contact Dermatitis.* 2011;64:220–228.
6. Burdick AE, Mathias T. The contact urticaria syndrome. *Dermatol Clin.* 1985;3:71–84.
7. Maibach HI. Immediate hypersensitivity in hand dermatitis: Role of food contact dermatitis. *Arch Dermatol.* 1976;112:1289–1291.
8. Hannuksela M. Atopic contact dermatitis. *Contact Dermatitis.* 1980;6:30.
9. Veien NK, Hattel T, Justesen O, Norholm A. Dietary restrictions in the treatment of adult patients with eczema. *Contact Dermatitis.* 1987;17: 223–228.
10. Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis.* 1976;2:28–42.
11. Doutre M-S. Occupational contact urticaria and protein contact dermatitis. *Eur J Dermatol.* 2005;15(6):419–424.
12. Elpern DJ. The syndrome of immediate reactivities (contact urticaria syndrome). An historical study from a dermatology practice. I. Age, sex, race and putative substances. *Hawaii Med J*. 1985;44:426–439.
13. Rudzki E, Rebanel P. Occupational contact urticaria from penicillin. *Contact Dermatitis.* 1985;13:192.
14. Nilsson E. Contact sensitivity and urticaria in "wet" work. *Contact Dermatitis.* 1985;13:321–328.
15. Veien NK, Hattel T, Justesen O, Norholm A. Dietary restrictions in the treatment of adult patients with eczema. *Contact Dermatitis.* 1987;17:223–228.
16. Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. *Contact Dermatitis.* 1987;17:270–275.
17. Weissenbach T, Wutrich B, Weihe WH. Allergies to laboratory animals. An epidemiological, allergological study in persons exposed to laboratory animals. *Schweiz Med Wochenschr.* 1988;118:930–938.
18. Doutre MS. Occupational contact urticaria and protein contact dermatitis. *Eur J Dermatol.* 2005;15:419–424.
19. Kanerva L, Jolanki R, Toikkanen J. Frequencies of occupational allergic diseases and gender differences in Finland. *Int Arch Occup Environ Health.* 1994;66:111–116.
20. Kanerva L, Toikkanen J, Jolanki R, Estlander T. Statistical data on occupational contact urticaria. Contact Dermatitis. 1996;35:229–233.
21. Kanerva L, Jolanki R, Toikkanen J, Estlander T. Statistics on occupational contact urticaria. In: Amin S, Lahti A, Maibach HI, editors. *Contact Urticaria Syndrome.* Boca Raton, FL: CRC Press, 1997; p. 57–69.
22. Williams JD, Lee AY, Matheson MC, Frowen KE, Noonan AM, Nixon RL. Occupational contact urticaria: Australian data. Br J Dermatol. 2008;159:125–131.
23. Teo S, Teik-Jin Goon A, Siang LH, Lin GS, Koh D. Occupational dermatoses in restaurant, catering and fast-food outlets in Singapore. *OccupMed* (Lond). 2009;59:466–471.
24. Bourrain JL. Occupational contact urticaria. *Clin Rev Allergy Immunol*. 2006;30:39–46.
25. Susitaival P, Flyvholm MA, Meding B et al. Nordic Occupational Skin questionnaire (NOSQ-2002): A new tool for surveying occupational skin diseases and exposure. *Contact Dermatitis.* 2003;49:70–76.

26. Mathias CG. Contact dermatitis and workers' compensation: Criteria for establishing occupational causation and aggravation. *J Am Acad Dermatol.* 1989;20:842–848.
27. Von Krogh C, Maibach HI. The contact urticaria syndrome. An update review. *J Am Acad Dermatol.* 1981;5:328–342.
28. Kligman AM. Dimethyl sulphoxide I and II. J Am Med Assoc. 1965;193:796–804, 923–928.
29. Lahti A, Oikarinen A, Viinikka L, Ylikorkala O, Hannuksela M. Prostaglandins in contact urticaria induced by benzoic acid. *Acta Dermatol Venereol* (Stockh). 1983;63:425–427.
30. Lahti A, Vaananen A, Kokkonen E-L, Hannuksela M. Acetylsalicylic acid inhibits non-immunologic contact urticaria. *Contact Dermatitis.* 1987;16:133–135.
31. Johansson J, Lahti A. Topical non-steroidal anti-inflammatory drugs inhibit non-immunological immediate contact reactions. *Contact Dermatitis.* 1988;19:161–165.
32. Morrow JD, Minton TA, Awad JA, Roberts LJ. Release of markedly increased quantities of prostaglandin D2 from the skin in vivo in humans following the application of sorbic acid. *Arch Dermatol.* 1994;130:1408–1412.
33. Downard CD, Roberts LJ, Morrow JD. Topical benzoic acid induces the increased synthesis of prostaglandin D2 in humans skin in vivo. *Clin Pharmacol Ther.* 1995;74:441–445.
34. Lundblad L, Lundberg JM, Anggard A, Zetterstrom O. Capsaicin sensitive nerves and the cutaneous allergy reaction in man. Possible involvement of sensory neuropeptides in the flare reaction. *Allergy.* 1987;42:20–25.
35. Lahti A, Maibach HI. Long refractory period after application of one nonimmunologic contact urticaria agents to the guinea pig ear. J Am Acad Dermatol. 1985;13:585–589.
36. Lovell CR. Urticaria due to plants. In: Lovell CR, editor. *Plants and the Skin*. Oxford: Blackwell Science Ltd., 1993; p. 29–41.
37. Amaro C, Goossens A. Immunological occupational contact urticaria and contact dermatitis from proteins: A review. *Contact Dermatitis.* 2008;58:67–75.
38. Lahti A, Björksten F, Hannuksela M. Allergy to birch pollen and apple, and crossreactivity of the allergens studied with RAST. *Allergy.* 1980;35:297.
39. Löwenstein H, Eriksson NE. Hypersensitivity to foods among birch pollen-allergic patients. *Allergy.* 1983; 38:577.
40. Dreborg S, Foucard T. Allergy to apple, carrot and potato in children with birch pollen allergy. *Allergy.* 1983;38:167.
41. Kanerva L, Estlander T. Immediate and delayed skin allergy from cow dander. *Am J Contact Dermat.* 1997;8:167–169.
42. Conde-Salazar L, Gonzalez MA, Guimaraens D. Type I and type IV sensitization to Anisakis simplex in 2 patients with hand eczema. *Contact Dermatitis.* 2002;46:361.
43. Tupasela O, Kanerva L. Skin tests and specific IgE determinations in the diagnostics of Contact urticaria caused by low-molecular-weight chemicals. In: Amin S, Lahti A, Maibach HI, editors. *Contact Urticaria Syndrome.* Boca Raton, FL: CRC Press, 1997; p. 33–44.
44. Cromwell O, Pepys J, Parish WE, Hughes EG. Specific IgE antibodies to platinum salts in sensitized workers. *Clin Allergy.* 1979;9:109.
45. Estlander T, Kanerva L, Tupasela O, Heskinen H, Jolanki R. Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis. *Clin Exp Allergy.* 1993;23:306.
46. Lahti A. Non-immunologic contact urticaria. *Acta Dermatol Venereol* (Stockh). 1980;60(Suppl.):3–49.
47. Clemmenson O, Hjorth N. Perioral contact urticaria from sorbic acid and benzoic acid in a salad dressing. *Contact Dermatitis.* 1982;8:1–6.
48. Kligman AM. The spectrum of contact urticaria: Wheals, erythema and pruritus. *Dermatol Clin.* 1990;8:57–60.
49. Babilas P, Landthaler M, Szeimies RM Anaphylactic reaction following hair bleaching. *Hautarzt* 2005; 56:1152–1155.
50. Barbaud A. Urticarires de contact. *Ann Dermatol Venereol*. 2002;128:1161–1165.
51. Von Krogh G, Maibach HI. Contact urticaria. In: Adam RM, editor. *Occupational Skin Disease*. New York: Grune & Stratton, 1983; p. 58–69.
52. Bonnevie P. Occupational allergy in bakery. In:, Stenfert-Kroese WF, editor. *European Academy of Allergy Occupational Allergy*. Springfield, IL: CC Thomas, 1958; p. 161–168.
53. Herxheimer H. Skin sensitivity to flour in baker's apprentices. *Lancet.*1967;1:83–84.

54. Herxheimer H. The skin sensitivity to flour of baker's apprentices: A final report of long term investigation. *Acta Allergol.* 1967;28:42–49.
55. Nutter AF. Contact urticaria to rubber. *Br J Dermatol.*1979;101: 597–598.
56. Hjorth N. Occupational dermatitis in the catering industry. Br J Dermatol. 1981;105:37.
57. Sutton R, Skerritt JH, Baldo BA, Wrigley CW. The diversity of allergens involved in baker's asthma. *Clin Allergy.* 1984;14:93–107.
58. Jagtman BA. Urticaria and contact urticaria due to basic blue 99 in a hair dye. *Contact Dermatitis.* 1996;35:52.
59. Torresani C, Periti I, Beski L. Contact urticaria syndrome from formaldehyde with multiple physical urticarias. *Contact Dermatitis.* 1996;35:174–175.
60. Escribano M, Muñoz-Bellido FJ, Velazquez E et al. Contact urticaria due to aescin. *Contact Dermatitis*. 1997;37:233–253.
61. Gutierrez D, Conde A, Duran S et al. Contact urticaria from lupin. *Contact Dermatitis.* 1997;36:311.
62. Brehler R, Sedlmayr S. Contact urticaria due to rubber chemicals? *Contact Dermatitis*. 1997;37:125–127.
63. Geyer E, Kränke B, Derhaschnig J, Aberer W. Contact urticaria from roe deer meet and hair. *Contact Dermatitis*. 1998;39:34.
64. Cancian M, Fortina AB, Peserico A. Contact urticaria syndrome from constituents of balsam of Peru and fragrance mix in a patient with chronic urticaria. *Contact Dermatitis.* 1999;41:300.
65. Kalogeromitros D, Armenaka M, Katsarou A. Contact urticaria and systemic anaphylaxis from codfish. *Contact Dermatitis.* 1999;41:170.
66. Schalock PC, Storrs FJ, Morrison L. Contact urticaria from panthenol in a hair conditioner. *Contact Dermatitis*. 2000;43:223.
67. Foti C, Nettis E, Panebianco R, Cassano N, Diaferio A, Porzia Pia D. Contact urticaria from Matricaria chamomilla. *Contact Dermatitis*. 2000;42:360–361.
68. Le Coz CJ, Ball C. Contact urticaria syndrome from mustard in anchovy fillet mustard sauce. *Contact Dermatitis.* 2000;42:114–115.
69. Guin JD, Goodman J. Contact urticaria from benzyl alcohol presenting as intolerance to saline soaks. *Contact Dermatitis*. 2001;45:182–183.
70. Yamakawa Y, Ohsuna H, Aihara M, Tsubaki K, Ikezawa Z. Contact urticaria from rice. *Contact Dermatitis*. 2001;44:91–93.
71. Porcel S, León F, Cumplido J, Cuevas M, Guimaraens D, Conde-Salazar L. Contact urticaria caused by heat-sensitive raw fish allergens. *Contact Dermatitis*. 2001;45:139–142.
72. Conde-salazar L, Guimaraens D, Gonzalez MA, Mancebo E. Occupational allergic contact urticaria from amoxicillin. *Contact Dermatitis.* 2001;45:109.
73. Kanerva L, Vanhanen M. Occupational allergic contact urticaria and rhinoconjunctivitis from a detergent protease. *Contact Urticaria.* 2001;45:49–51.
74. Hernández B, Ortiz-Frutos FJ, Garcia M, Palencia S, Garcia MC, Iglesias L. Contact urticaria from 2-phenoxyethanol. *Contact Dermatitis*. 2002;47:54.
75. Narayan S, Sanson JE. Contact urticaria from runner bean (Phaseolus coccineus). *Contact Dermatitis*. 2002;47:243.
76. Sugiura K, Sugiura M, Shiraki R et al. Contact urticaria to polyethylene gloves. *Contact Dermatitis.* 2002;46:262–266.
77. Sugiura K, Sugiura M, Hayakawa R, Shamoto M, Sasaki K. A case of contact urticaria syndrome due to di(2-ethylhexyl)phatalete (DOP) in work clothes. *Contact Dermatitis*. 2002;46:13–16.
78. Hannuksela M. Mechanisms in contact urticaria. *Clin Dermatol*. 1997;15: 619–622.
79. Suzuki T, Kawada A, Yashimoto Y, Isogai R, Aragane Y, Tezuka T. Contact urticaria to ketoprofen. Contact Dermatitis. 2003;48:284–285.
80. Diva VC, Statham BN. Contact urticaria from cinnamal leading to anaphylaxis. *Contact Dermatitis.* 2003; 48:119.
81. Bourrain JL, Amblard P, Béani JC Contact urticaria photoinduced by benzophenones. *Contact Dermatitis.* 2003;48:45–46.
82. Monteseirín J, Pérez- Formoso JL, Hérnandez M et al. Contact urticaria from dill. *Contact Dermatitis.* 2003;48:275.