

Metal Allergy—A Review on Exposures, Penetration, Genetics, Prevalence, and Clinical Implications

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The prevalence of metal allergy is high in the general population, and it is estimated that up to 17% of women and 3% of men are allergic to nickel and that 1–3% are allergic to cobalt and chromium. Among dermatitis patients, the prevalence of metal allergy is even higher. Metal allergy is mainly an environmental disorder although null mutations in the filaggrin gene complex were recently found to be associated with nickel allergy and dermatitis. Environmental metal exposures include jewelry, buttons, clothing fasteners, dental restorations, mobile phones, and leather. Although consumer exposure is responsible for most cases of metal allergy, the importance of occupational metal exposure remains present and should always be taken into consideration when one interprets allergic patch test reactions to metals. Traditionally, nickel, cobalt, and chromium have been the most important contact allergens. However, recently, gold and palladium have drawn much attention as the prevalence of contact allergy to these metals is high. Palladium allergy is mainly a result of cross-sensitization to nickel, whereas gold allergy is rarely clinically relevant when one takes its high prevalence into account. The epidemiology of metal allergy has recently changed in Europe as nickel allergy among ear-pierced Danish women has decreased following regulatory intervention on nickel release from consumer products. In the United States, the prevalence of nickel allergy is still increasing, which may be explained by the absence of regulation. The prevalence of chromium allergy is increasing in the United States, Singapore, and Denmark among dermatitis patients. This increase is significantly associated with leather exposure in Denmark. Metal allergy may result in allergic contact dermatitis and systemic allergic (contact) dermatitis. Furthermore, metal allergy has been associated with device failure following insertion of intracoronary stents, hip and knee prostheses, as well as other implants. This area is in need of more research.

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1. Introduction

Metals such as nickel, cobalt, and chromium are ubiquitous in our environment. Over the 20th century, industrialization and modern living have resulted in increased cutaneous exposure to these metals and hence metal allergy (1, 2). This review aims

Table 1. Metals That Most Often Result in Contact Allergy and Allergic Contact Dermatitis

metal	magnitude of clinical problem
nickel	major
cobalt	
chromium	
gold	rising?
palladium	
aluminum	

to briefly update the reader on past and current metal exposures, metal skin penetration, genetic predisposition, recent epidemiological trends, and the clinical implications of metal contact. It has an overall focus on nickel, cobalt, and chromium, as these metals are the most prevalent contact allergens and as they are included in the European and North American baseline patch test series. Other metals like gold, palladium, and aluminum will only be sparsely discussed (Table 1).

2. Causative Metal Exposures

2.1. Nickel. Over the first half of the 20th century, nickel allergy and dermatitis were mainly observed among workers in the plating industry (3, 4). However, the large number of nickel-allergic people seen today is mainly explained by exposure to nickel-releasing consumer items. Metals that release nickel include white gold, gold plating, German silver, Monel solder, nickel plating, and stainless steel. The nickel epidemic began in the 1950–1960s with an increasing number of female dermatitis patients who had eruptions at the site of their stocking

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suspenders (5). In the 1970–1980s, nickel release from jean buttons and zippers resulted in dermatitis in both genders (6, 7). In the 1980s, the popularity of ear piercing and the use of nickel-plated jewelry lead to nickel allergy and dermatitis in a large proportion of women (8–11). Thus, in 1990, the Danish government restricted nickel release from consumer items such as jewelry, buttons, and zippers to prevent nickel allergy (1, 12). In 1994, the EU Nickel Directive was passed to protect European citizens from nickel allergy (1994/27/EC). This intervention rapidly lead to a significant decrease in the proportion of consumer items that released an excessive amount of nickel ($>0.5 \mu\text{g nickel/cm}^2/\text{week}$) in Sweden (13, 14). Today, new sources of nickel allergy have been discovered, for example, in head sets, mobile phones, and children's clothing fasteners (15–17). In men, the number of body piercings is positively correlated with nickel allergy (18). A possible association between nickel allergy and nickel dermatitis following makeup exposure has been much debated; however, it remains unclear whether nickel-allergic subjects should avoid, for example, mascaras and eye shadows that contain nickel (19–21). Despite the changing patterns of consumer exposure, excessive nickel release is still frequent from jewelry. Recent Danish and American studies have shown that approximately 10–30% of inexpensive jewelry release nickel in concentrations that may result in sensitization and elicitation of dermatitis (22, 23). Likewise, approximately 20% of mobile phones from the Danish market in 2007 released excessive nickel concentrations (15). Mobile phones are now covered by the EU Nickel Directive (24).

Despite increased work hygiene, occupational nickel exposure may still result in morbidity. Shah et al. found that in 22.8% of 368 nickel-allergic dermatitis patients, nickel allergy had occupational relevance (25). The most common occupations were retail clerks, hairdressers, domestic cleaners, metal workers, and caterers (25). In line with this finding, 30.7% of 332 Polish patients with occupational contact dermatitis had clinically relevant nickel allergy (26). Furthermore, up to 12% of British patients diagnosed with occupational contact dermatitis had an occupationally relevant nickel allergy (27). Dickel et al. found that nickel was the most frequent sensitizer among patients with occupational skin disease but also that occupational relevance only was present in 11% (28). A recent Danish report described two female hairdressers with occupational nickel hand eczema following contact with scissors and crochet hooks that released excessive amounts of nickel (29). Lidén et al. found that nickel deposition on the hands in locksmiths, cashiers, and carpenters following work was capable of eliciting nickel dermatitis and possibly causing or contributing to sensitization (30). This was in accordance with a previous study that found excessive nickel release in 27% of 565 hand-held tools with metal parts that potentially came into contact with the skin (31). Finally, an Australian study showed that nickel was the most prevalent occupational allergen among female patients with dermatitis, whereas nickel only ranked 10 in men (32). Taken together, these reports underscore that occupational nickel allergy and dermatitis should always be suspected.

2.2. Chromium. Historically, the most important cause of chromium allergy has been occupational skin exposure to cement. The first cases of chromium dermatitis were reported among construction workers who built the Metro in Paris in 1908 (33). In the 1970s, Denmark saw an accumulation of persons with permanent disability due to chromium dermatitis from occupational cement exposure (34). However, the compulsory addition of iron sulfate to cement in 1983 reduced the

amount of water-soluble hexavalent chromium as well as the prevalence of chromium allergy among construction workers in Denmark (35, 36). In 2005, an EU Directive (2003/53/EC) restricting the marketing and use of cement containing more than 2 ppm hexavalent chromium came into force in the member states. Although chromium dermatitis remains prevalent in countries with a high number of construction workers (37), the addition of iron sulfate to cement has resulted in significantly lower urinary chromium concentrations in Taiwanese cement workers with hand dermatitis (38). Occupational chromium allergy remains associated with male gender and older age (39), and it is estimated that occupational chromium exposure played a role in 6% of 22184 British patients with occupational contact dermatitis (40). In Australia, chromium allergy affected 37% of male patients with occupational contact dermatitis (32). Besides cement exposure, occupational chromium exposure may derive from contact with dyeing agents, metal alloys, pottery colorants, and antirust agents in coolants (40). Lidén et al. showed that chromium was deposited on the hands in especially locksmiths (chromium mean = $0.045 \mu\text{g/cm}^2/\text{h}$) but also in carpenters and cashiers (chromium mean = $0.003\text{--}7 \mu\text{g/cm}^2/\text{h}$) (30). Geier et al. showed that handling of chromated metal products such as screws and fittings was a hazard to chromium-allergic subjects, in particular those with a strong sensitization (41).

Recently, chromium exposure has changed from an occupational problem to a consumer problem (42). In Denmark, the frequency of relevant leather exposure among chromium-allergic patients increased from 24.1% during 1989–1994 to 45.5% during 1995–2007 ($p < 0.02$) (42). At the same time, the frequency of clinically relevant cement exposure decreased among chromium-allergic patients from 12.7% in 1989–1994 to 3.0% in 1995–2007 ($p < 0.01$) (42). Today, nearly 90% of the global leather production is tanned using chromium sulfates (43). The German Federal Institute for Risk Assessment found that more than half of 850 leather goods contained hexavalent chromium and that one-sixth contained more than 10 mg chromium/kg leather (<http://www.bfr.bund.de/cd/9575>). Similarly, 35% of 43 leather products on the Danish market contained hexavalent chromium above the detection limit of 3 ppm (range, 4–15 ppm) (44). Today, it is accepted that most chromium-allergic patients are sensitized and develop contact dermatitis following consumer exposure to chromium in finished leather products (45–48).

2.3. Cobalt. Cobalt is used in the production of alloys, magnets, prosthetics, paints, pigments, and jewelry (49). High prevalences of cobalt allergy among women and female dermatitis patients have traditionally been explained by consumer exposure, as it used to be mixed with or occur as an impurity in nickel alloys used in jewelry (50). Also, higher prevalences of cobalt allergy have been observed in pierced men in comparison to nonpierced men (18, 51). Concomitant allergy to nickel and cobalt is generally explained by cosensitization rather than cross-reactivity (52, 53). Concomitant nickel and cobalt allergy has also been associated with more severe forms of dermatitis and non-Caucasian races (54, 55). Today, nickel and cobalt are found less frequently together as global cobalt prices have increased. In the 1970–1980s, the content of cobalt in household products was discussed as a cause of consumer cobalt allergy (56); however, only minor traces of cobalt are generally found in such products (57, 58). It is probable that the increasing use of cobalt in dental alloys is a source of sensitization that may have been previously overlooked (59).

Concomitant nickel and cobalt allergy has also been observed among hard metal workers with hand eczema, as a British study found that 25% had concomitant cobalt and nickel allergy (55). Furthermore, isolated cobalt allergy has been observed among hard metal workers and painters in the glass and pottery industries (60, 61). In Australia, cobalt allergy was the second most prevalent contact allergy among male patients with occupational contact dermatitis (11%) and the 10th most important in female patients (5.7%) (32). In the United Kingdom, cobalt allergy had clinical relevance in 4% of 22184 patients with occupational contact dermatitis (40). Cobalt allergy was associated with increasing age in men but not in women (40). Lidén et al. showed that cobalt was only deposited to a little degree on the hands in locksmiths, carpenters, cashiers, and secretaries (cobalt mean = $0.0001\text{--}2\text{ }\mu\text{g}/\text{cm}^2/\text{h}$) (30).

2.4. Gold, Palladium, and Aluminum. Palladium and gold are typically used in dental restorations and jewelry (49). Gold has also been used for coronary stents and rheumatic therapy (62). Occupational palladium exposure may occur in the electronics and chemical industries. Aluminum allergy is traditionally associated with occupational exposure (49) but is also a content of some hypersensitization therapies (63).

3. Metal Penetration

Metal allergy is developed following repeated or prolonged skin contact with metal ions. Before metal ions can elicit a cutaneous immune response, they must gain access to the viable epidermis. Thus, they should have certain physicochemical characteristics that are necessary for passage across the stratum corneum, as it normally works as an effective barrier to many chemicals (64). Exogenous (e.g., dose, size, counterions, polarity, valence, and pH) and endogenous (e.g., age of the skin, anatomical site, oxidation, and reduction) factors are important and should also be accounted for when investigating metal absorption (65–67). Nickel is mostly accumulated in the stratum corneum, and only minor amounts are found in the lower layer of epidermis (68, 69). It is estimated that more than 90% of available nickel ions are in a bound state (68). Only trivalent and hexavalent chromium are sufficiently stable to act as haptens. Hexavalent chromium may easily pass through the epidermis, whereas trivalent chromium tends to form stable complexes within the epidermis (70, 71). Once hexavalent chromium has entered the skin, it is reduced to trivalent chromium, which then binds to proteins. Little is known about cobalt absorption; however, it has been shown that volunteers who were cutaneously exposed to cobalt had higher concentrations of urinary cobalt (72). Also, it has been shown that the permeation of both nickel and cobalt ions may be closely associated with the oxidizing capacity of sweat (65, 73). It was recently demonstrated that cobalt and nickel powders penetrate damaged skin more easily than intact skin but also that chromium probably has a stronger skin protein binding capacity (74–78). Filon et al. found that 99% of chromium accumulated in the skin when performing in vitro skin permeation experiments (78). In their native state, metal ions are haptens and as such are of insufficient size to provoke an immune response. For this to be achieved, they must form stable conjugates with proteins once inside the skin (79). Consequently, contact allergens are either inherently protein-reactive or can be metabolized in the skin to protein-reactive species (80). However, it was recently shown that some contact allergens, for example, nickel, may interact directly with the human histocompatibility leukocyte antigen (HLA) in a peptide-independent manner (81).

4. Genetic Predisposition to Metal Allergy

A recent review found no definite genetic predisposition to nickel allergy (82). Of interest, previous epidemiological studies have found conflicting results. Thus, a Danish study with 1546 twins showed that nickel allergy was influenced by genetic factors since nickel allergy was more prevalent in monozygotic than dizygotic twins (11), whereas a more recent twin study found that nickel allergy was explained by environmental rather than genetic factors (83). Recently, null mutations in the filaggrin gene complex were found to be associated with nickel allergy as well as nickel allergy in combination with self-reported jewelry dermatitis among subjects from the general population (84). Filaggrin is a highly phosphorylated, histidine-rich polypeptide that aggregates keratin filaments and is a crucial component of the terminal differentiation of the epidermis (the outer layer of the skin). It prevents epidermal water loss and also impedes the entry of microorganisms, allergens, and chemicals (85). Loss of filaggrin expression may lead to deficiencies in the terminal formation of the stratum corneum and disrupt skin–barrier function. Many mutations in the FLG gene have so far been documented, and it is estimated that 10% of the general population is affected (86, 87). As histidine and histidine-rich polypeptides are strong nickel chelating agents, it is possible that the accumulation of nickel in the upper part of stratum corneum is partly caused by filaggrin (88). Thus, nickel may possibly permeate freely or more rapidly in filaggrin-deficient skin in comparison to normal skin. If so, different routes of nickel exposure may explain the contradictory results found in past twin studies. Thus, the majority of twins in the study by Menné and Holm were cutaneously exposed to nickel from stocking suspenders and buttons (11), whereas most twins in the study by Bryld et al. were rather exposed to nickel ions from ear piercing (83). In the latter case, the immune system was directly exposed to nickel ions as the skin and its compartments (including nickel chelating filaggrin) were bypassed by perforation. This may explain why no genetic predisposition could be found in the second twin study (88).

5. Prevalence and Trends

5.1. General Population. The prevalence of metal allergy is high in the general population. It is estimated that up to 17% of women and 3% of men are nickel allergic, whereas only 1–3% are allergic to cobalt and chromium (2, 50, 89–91). A recent study showed that the prevalence of nickel allergy was 33.8% among Thai women and that the prevalence was highest among 18–25 year olds (92). The higher prevalence in women is mainly explained by ear piercing (93), and it is estimated that 80% of women and 10% of men are ear-pierced (2). Two consecutive cross-sectional patch test studies from the same general population in Denmark showed that the prevalence of chromium and cobalt allergy decreased significantly between 1990 and 2006 (94). The decrease of chromium allergy was mainly explained by an effect of the Danish chromium regulation, which reduced the amount of water-soluble hexavalent chromium in cement, and by increased work hygiene. The decrease of cobalt allergy was mainly observed in women and was probably a result of reduced exposure to cobalt (and nickel) from inexpensive jewelry (94). Furthermore, the epidemiology of nickel allergy has recently changed among women from the general population in Denmark. This change is likely to be explained by the 1990 regulatory intervention on nickel allergy (12). Thus, a significantly ($p = 0.004$) lower prevalence of nickel allergy was found among Danish women pierced after the nickel

regulation came into effect (6.9%) in comparison to women ear-pierced before 1990 (16.6%) (95).

5.2. Clinical Patients. Among 19793 patients from 10 European patch test centers, the age- and sex-standardized prevalences of nickel, cobalt, and chromium allergies were 19.7–24.5, 6.2–8.8, and 2.4–5.9%, respectively, for the period 2005–2006 (96). Gold allergy may be observed in up to 10% of dermatitis patients (97, 98) and 30–37% of dental and cardiac patients (62, 99); palladium allergy may be seen in up to 10% of dermatitis patients (100–103), whereas aluminum allergy is only observed in very few patients (63, 104). Recently, the epidemiology of nickel allergy has diverged in Europe and North America. In Denmark and Germany, significantly decreasing prevalences of nickel allergy have been observed among young female patients following the regulatory interventions on nickel exposure (16, 105, 106). In the United States and Canada, there are currently no regulations on nickel exposure, and contact allergy surveillance has recently demonstrated increasing prevalences of nickel allergy, which is now debated (107, 108). It has been speculated whether the EU Nickel Directive could result in increased use of cobalt in jewelry and hence cobalt allergy (109). However, a recent Danish 23 year retrospective patch test study did not support such a trend, although the prevalence of cobalt allergy among young female patients did not follow the decrease observed for nickel allergy (106). The prevalence of palladium allergy increased in Italy over a 10 year period; however, the vast majority of cases were polysensitized (92%), suggesting cross-sensitization (110). The increase could possibly be a result of the increasing popularity of white gold, although this is speculative. Finally, the epidemiology of chromium allergy is changing in Denmark as the prevalence is increasing significantly in both genders due to leather exposure (42). Similar increases have also been observed in the United States and in Singapore, although their causes were not determined (111, 112).

6. Coreactivity and Clinical Relevance

Metal coreactivity is common among dermatitis patients. Data analysis of 11516 patch-tested patients showed that 79% of cobalt-allergic patients, 39% of chromium-allergic patients, and 95% of palladium-allergic patients, respectively, also reacted to nickel (103). Furthermore, 23% of nickel-allergic patients, 31% of chromium-allergic patients, and 36% of palladium-allergic patients, respectively, also reacted to cobalt (103). Finally, 5% of nickel-allergic patients and 15% of cobalt-allergic patients also displayed a positive reaction to chromium (103). From the above, it can be appreciated that both cross-sensitization (e.g., nickel and palladium) and concomitant sensitization (e.g., nickel and cobalt) may occur. Dermatologists should therefore always critically interpret positive patch test reactions and determine clinical relevance, that is, present, past, or unknown.

The clinical relevance of metal allergy is highly dependent on the metal in question. Nickel, cobalt, and chromium allergy are usually of clinical relevance (either past or present), although it has been postulated that isolated cobalt allergy may reflect a general skin vulnerability rather than a relevant allergic reaction (60). In this study, Rystedt found that 1.2% of 4034 dermatitis patients reacted to cobalt but not to nickel or chromium. However, she found that the majority of these patients also reacted to other contact allergens such as rubber chemicals or had atopic dermatitis. There is currently limited evidence to support that isolated cobalt reactions represent skin vulnerability

rather than true allergic skin reactions, although false positive reactions to cobalt do occur (113, 114).

Despite the fact that there has been a general change of attitude, gold allergy is rarely clinically relevant when one takes its high prevalence into account. Gold dermatitis may be observed at the site of jewelry contact (115–117), although it has been shown that gold-allergic female dermatitis patients who avoided gold earrings did not experience improvement of their earlobe dermatitis (118). Furthermore, it has been reported that gold-allergic patients may develop eyelid dermatitis (119, 120), which supposedly is caused by cosmetic powders that abrade jewelry and act as carriers to the face (118). Finally, gold allergy is more common in patients with gold dental restorations and gold coronary stents (62, 120, 121). Although gold allergy may be associated with mucosal disease (122), most gold-allergic patients tolerate gold restorations well (120). Palladium allergy is usually interpreted as a result of cross-sensitization to nickel. In a randomized study, patients with nickel and palladium allergy had flare-up reactions on sites previously tested with nickel and palladium following oral nickel provocation (123). A correlation between high nickel sensitivity and reactivity to palladium was found among 462 nickel allergic dermatitis patients (124). Despite these convincing reports, sarcoidal type allergic contact granuloma due to palladium exposure and allergy may occur in a few patients (125). Finally, aluminum allergy has been observed in children with persistent subcutaneous nodules who underwent hyposensitization therapy (63). The subcutaneous nodules were considered to be cutaneous manifestations of contact allergy.

7. Clinical Implications

7.1. Allergic Contact Dermatitis. Two distinct phases are recognized at the mechanistic level, an induction phase and an elicitation phase. The induction phase usually develops over a few days to some weeks and includes the immunological events following first skin contact with the metal. This phase is complete when antigen specific T-cells have been developed and the individual is sensitized (126). The effector phase usually develops within 1–2 days but may already take place within 2 h (126). Activation of antigen specific T-cells results in dermatitis at the site of allergen skin contact, and the reaction usually resolves within days to weeks. At the clinical level, the induction phase is referred to as contact sensitization or contact allergy, whereas the effector phase is referred to as allergic contact dermatitis (126). Contact allergy is considered to be a chronic and potentially life-long condition (127). Allergic contact dermatitis may involve all body parts (Figure 1). Nickel and cobalt dermatitis are typically seen on the face (earlobes), body (at sites of jewelry and piercings), and hands, whereas chromium dermatitis is located on the hands and feet. The clinical picture varies depending on its chronicity. Acute dermatitis is characterized by erythema, edema, papules, vesicles, and weeping, whereas chronic dermatitis is scaly, dry, and fissured. Risk factors of allergic contact dermatitis include the inherent sensitizing potential of an allergen (128), elevated allergen concentration (dose per unit area) (129), high frequency of exposure (130), occlusion (131), long exposure time (132), the presence of penetration enhancing factors, and an altered skin barrier function (133). Studies have shown that the prognosis of dermatitis is especially poor for chromium-allergic patients (38, 134–136). Also, the prognosis of nickel dermatitis is improved in patients where nickel contact is limited or avoided (137).



Figure 1. Mild allergic nickel dermatitis caused by nickel release from a belt buckle.

Over the years, various binding agents and barrier creams have been investigated for their ability to prevent allergic metal dermatitis (138–140). The use of 10–15% disodium ethylenediamine tetra-acetate (EDTA) in a cream was successful at reducing nickel patch test reactivity in nickel-allergic patients but not at reducing chromium patch test reactivity in chromium-allergic patients (74, 138, 140–142). Bidentate sulfur donor ligands such as diethyldithiocarbamate and tetraethylthiuram (disulfiram) disulfide have been investigated for their nickel chelating abilities (143, 144). A placebo-controlled double-blinded study found that oral disulfiram treatment was relatively effective at reducing nickel dermatitis but also that hepatotoxicity was frequently observed (143). For these reasons, disulfiram is rarely used in a clinical setting. A study found that 5-chloro-7-iodoquinolin-8-ol (clioquinol) was the most effective ligand for the prevention of allergic nickel dermatitis to nickel when compared with EDTA (15%), ascorbic acid (20%), and α -tocopherol (10%) (141). Thus, when 20 pence coins were coated with cream containing 3% clioquinol and 1% hydrocortisone and used for patch testing in 26 nickel-allergic subjects, no dermatitis reactions were observed after 2 days of occlusion (141). Because clioquinol may penetrate the skin and result in neurotoxicity and blindness (145), the ligand is usually not applied for the prevention of nickel dermatitis. Furthermore, anion and cation exchangers have proven to be effective for the prevention of dermatitis in chromium- and nickel-allergic patients, respectively (146). The advantage of cation exchange resins in comparison to ligands is their inability to absorb through the skin. A polyurethane coating of consumer items worn close to the skin (e.g., jean buttons, bracelets, and watches) may prevent nickel dermatitis in nickel-allergic individuals (147, 148). Finally, a randomized, double-blind study found that a 10% diethylenetriaminepentaacetic acid (DTPA) cream abrogated positive patch test reactions in nickel-, cobalt-, and copper-sensitized subjects but not in palladium- and chromium-allergic patients (139).

Dose-response studies have been performed for nickel, cobalt, and chromium. Nickel elicitation studies have revealed that approximately 5% of a nickel-sensitized population will react to an occluded (e.g., wrist watch and buttons) dose of $0.44 \mu\text{g}$ nickel/cm²/week and also that the allergy and elicitation thresholds for skin-penetrating exposure (e.g., earrings) are lower (149). Basketter et al. investigated safe levels of nickel in consumer products (e.g., cosmetics and household products) and

found that products should not contain more than 5 ppm of nickel and that the ultimate target level should be 1 ppm (57, 58). Fischer et al. recently showed that elicitation of nickel allergy depended on the size of the exposed area (and therefore the total amount of applied nickel) even though the same dose per unit area was applied (150). Chromium elicitation studies have suggested that hexavalent chromium concentrations between 0.6 and 1770 ppm and trivalent chromium concentrations between 89 and 25350 ppm may elicit chromium dermatitis (74, 151, 152). A review including six hexavalent chromium dose-response studies concluded that 10% of chromium-allergic patients will react to 7–44 ppm hexavalent chromium (corresponding to $0.35\text{--}0.9 \mu\text{g}/\text{cm}^2/48 \text{ h}$) when patch tested (153). Obviously, many chromium-allergic patients tolerate higher doses. Finally, cobalt elicitation studies have demonstrated that cobalt-allergic patients may react to even very low concentrations of cobalt. Juliander et al. showed that 4 of 19 cobalt-allergic dermatitis patients reacted to 320 ppm cobalt upon patch testing, the lowest concentration used in their serial dilution (114). Another study with 72 cobalt-allergic patients identified an elicitation concentration at 50 ppm (154), whereas Fischer and Rystedt found that cobalt-allergic patients could react to cobalt test concentrations at 19 ppm (61). Finally, Allensby and Basketter showed that when the site of patch testing in cobalt-allergic dermatitis patients was pretreated for 24 h with a surfactant, 3 of 6 patients reacted to 10 ppm cobalt upon testing (155).

7.2. Systemic Allergic (Contact) Dermatitis. Systemic allergic dermatitis describes a cutaneous eruption following systemic exposure to an allergen. The possible pathomechanisms of systemic allergic dermatitis have recently been reviewed (156). A study on systemic nickel allergy found a dose-response relationship between nickel ingestion and dermatitis flare-up (157). Thus, 0.3, 1, and 4 mg nickel sulfate hexahydrate gave dermatitis in 40, 40, and 70% of nickel-allergic subjects. From this study, it can be concluded that a single dose of 4 mg nickel will result in widespread dermatitis in most nickel-allergic patients (157). However, another oral nickel exposure study found that some nickel-allergic patients developed tolerance in response to increasing nickel doses (158). Low-nickel diets or nickel-chelating drugs may result in clearing or improvement of dermatitis in nickel-allergic patients (144, 159). Systemic exposure to chromium, cobalt, and gold may also result in systemic allergic dermatitis (160–162). Recently, systemic allergic dermatitis was reported following nickel release (μg) from small metallic eyelets at the base of the polyurethane peripheral intravenous catheters (163).

7.3. Implant Failure. Little is currently known about the possible association between metal release, metal allergy, and device failure. However, all metals in contact with body fluids corrode, and the released metal ions (haptens) may bind to proteins and activate T-cells (164, 165). This may in a few cases result in allergic contact dermatitis in the skin overlying the implants (166, 167) and even in device failure. It has been suggested that device failure is explained by activation of the inflammasome danger signaling pathway in human macrophages (168), but there may be many other involved pathomechanisms.

The majority of intracoronary stents are made from stainless steel, which contains nickel, chromium, and molybdenum. Coronary in-stent restenosis has been associated with nickel allergy in some studies (169–171), whereas others have not been able to confirm such an association (172–174). Gold allergy has also been associated with restenosis in patients who had gold-plated stents, and the use of gold has therefore been largely abandoned (62). Today, total hip arthroplasties may be

Table 2. Main Findings**Exposures**

- Nickel allergy mainly derives from skin contact with consumer items such as jewelry, mobile phones, clothing fasteners, buttons, and belt buckles and only to a smaller degree from occupational exposure.
- Chromium allergy derives from both occupational exposure to cement and metals and consumer exposure to leather goods.
- Cobalt allergy mainly derives from exposure to jewelry, alloys, metals, prostheses, dental restorations, and paints.
- Gold allergy derives from jewelry, dental restorations, rheumatic therapy, and coronary stents.
- Palladium allergy derives from dental restorations and jewelry.

Penetration

- Most nickel ions are bound in the stratum corneum.
- Nickel and cobalt powders penetrate damaged skin more easily than intact skin.
- Sweat may accelerate skin permeation of nickel and cobalt ions.

Genetic Predisposition

- Null mutations in the filaggrin gene complex may be associated with nickel allergy.

Prevalence and Epidemiological Trends

- Nickel allergy is observed in up to 17% of women and 3% of men. Cobalt allergy affects 1–3%.
- Nickel allergy is associated with ear piercings.
- Nickel allergy has decreased among Danish women and young female dermatitis patients following the 1990 regulatory intervention on consumer nickel exposure.
- Chromium allergy is currently increasing among Danish dermatitis patients due to leather exposure.

Clinical Relevance

- Metal coreactivity is highly frequent.
- Nickel, cobalt, and chromium allergies are usually of clinical relevance.
- Palladium and gold allergies are of clinical relevance in some cases.
- Metal allergy may result in allergic contact dermatitis, systemic allergic dermatitis, and possibly device failure.

performed using second generation metal-on-metal prostheses, which typically consist of a forged, high-carbon, cobalt–chromium–molybdenum material (175). They tend to produce a high load of metal particles in nanometer sizes, which accumulate to a high specific surface area (176). Recent studies have shown that patients with metal-on-metal prostheses may have elevated serum and urine concentrations of cobalt and chromium (176–180). This has resulted in increased concern about a possible association between metal allergy and implant failure (176, 181). Accumulated reports on metal allergy in total hip arthroplasty patients showed that the prevalence of metal allergy was ca. 25% among patients with well-functioning hip arthroplasties and 60% among patients with a failed or a poorly functioning implants (181). Despite these prevalences, which are much higher than general population estimates (2), it is uncertain whether metal allergy causes device failure or device failure causes metal allergy. Thomas et al. recently showed that among 16 patients with revised metal-on-metal arthroplasty and peri-implant lymphocytic inflammation, 81% had metal allergy based on patch testing and/or lymphocyte transformation testing LTT. Allergic reactions were mainly observed against cobalt, chromium, nickel, and molybdenum (182). The authors concluded that complications reflected allergic hyper-reactivity (182). Furthermore, few reports have shown severe clinical reactions such as “aseptic lymphocytic vasculitic associated lesions” (ALVAL) and “pseudotumours” following hip arthroplasty (183, 184). Metal-on-metal implants for hand joint replacement as well as total knee arthroplasties have also been associated with metal allergy (185, 186). In such instances, implants may be replaced with titanium-based endoprotheses (186). However, hypersensitivity reactions have also been

described following insertion of titanium implants, although titanium allergy is extremely rare (187).

8. Conclusion

Metal allergy remains prevalent (Table 2). The pattern of exposure has changed over the decades, mainly as result of regulatory interventions and increased work hygiene. Metal allergy remains of medical importance, lately illustrated by device failure.

References

- (1) Thyssen, J. P., Johansen, J. D., and Menné, T. (2007) Contact allergy epidemics and their controls. *Contact Dermatitis* 56 (4), 185–195.
- (2) Thyssen, J. P., Linneberg, A., Menné, T., and Johansen, J. D. (2007) The epidemiology of contact allergy in the general population—Prevalence and main findings. *Contact Dermatitis* 57 (5), 287–299.
- (3) Blascho, A. (1889) Die berufsdermatosen der arbeiter. Das galvanisierereizem. *Dtsch. Med. Wochenschr.* 15, 925–927.
- (4) Schittenhelm, A., and Stockinger, W. (1925) Über die idiosynkrasie gegen nickel (nickel krätze) und ihre beziehung zur anaphylaxie. *Z. Ges. Exp. Med.* 45, 58–74.
- (5) Calnan, C. D. (1956) Nickel dermatitis. *Br. J. Dermatol.* 68 (7), 229–236.
- (6) Brandrup, F., and Larsen, S. F. (1979) Nickel dermatitis provoked by buttons in blue jeans. *Contact Dermatitis* 5, 148–150.
- (7) Brandrup, F. (1991) Nickel eyelid dermatitis from an eyelash curler. *Contact Dermatitis* 25 (1), 77.
- (8) Boss, A., and Menné, T. (1982) Nickel sensitization from ear piercing. *Contact Dermatitis* 8, 211–213.
- (9) Fischer, T., Fregert, S., Gruvberger, B., and Rystedt, I. (1984) Nickel release from ear piercing kits and earrings. *Contact Dermatitis* 10 (1), 39–41.
- (10) Fischer, T., Fregert, S., Gruvberger, B., and Rystedt, I. (1984) Contact sensitivity to nickel in white gold. *Contact Dermatitis* 10 (1), 23–24.
- (11) Menné, T., and Holm, N. V. (1983) Nickel allergy in a female twin population. *Int. J. Dermatol.* 22 (1), 22–28.
- (12) Menné, T., and Rasmussen, K. (1990) Regulation of nickel exposure in Denmark. *Contact Dermatitis* 23 (1), 57–58.
- (13) Lidén, C., and Norberg, K. (2005) Nickel on the Swedish market. Follow-up after implementation of the Nickel Directive. *Contact Dermatitis* 52 (1), 29–35.
- (14) Lidén, C., and Johnsson, S. (2001) Nickel on the Swedish market before the Nickel Directive. *Contact Dermatitis* 44 (1), 7–12.
- (15) Thyssen, J. P., Johansen, J. D., Zachariae, C., and Menné, T. (2008) The outcome of dimethylglyoxime testing in a sample of cell phones in Denmark. *Contact Dermatitis* 59 (1), 38–42.
- (16) Thyssen, J. P., Hald, M., Avnstorp, C., Veien, N., Lauerberg, G., Nielsen, N. H., Kaaber, K., Kristensen, B., Kristensen, O., Thormann, J., Vissing, S., Menné, T., and Johansen, J. D. (2009) Characteristics of nickel allergic dermatitis patients seen in private dermatology clinics in Denmark: A questionnaire study. *Acta Derm.-Venereol.* 89, 384–388.
- (17) Heim, K. E., and McKean, B. A. (2009) Children’s clothing fasteners as a potential source of exposure to releasable nickel ions. *Contact Dermatitis* 60 (2), 100–105.
- (18) Ehrlich, A., Kucenic, M., and Belsito, D. V. (2001) Role of body piercing in the induction of metal allergies. *Am. J. Contact Dermatitis* 12 (3), 151–155.
- (19) Goh, C. L., Ng, S. K., and Kwok, S. F. (1989) Allergic contact dermatitis from nickel in eyeshadow. *Contact Dermatitis* 20 (5), 380–381.
- (20) van Ketel, W. G., and Liem, D. H. (1981) Eyelid dermatitis from nickel contaminated cosmetics. *Contact Dermatitis* 7 (4), 217.
- (21) Zemba, C., Romaguera, C., and Vilaplana, J. (1992) Allergic contact dermatitis from nickel in an eye pencil. *Contact Dermatitis* 27 (2), 116.
- (22) Thyssen, J. P., and Maibach, H. I. (2008) Nickel release from earrings purchased in the United States: The San Francisco earring study. *J. Am. Acad. Dermatol.* 58 (6), 1000–1005.
- (23) Thyssen, J. P., Menné, T., and Johansen, J. D. (2009) Nickel release from inexpensive jewelry and hair clasps purchased in an EU country—Are consumers sufficiently protected from nickel exposure? *Sci. Total Environ.* 407, 5315–5318.
- (24) Thyssen, J. P., and Johansen, J. D. (2009) Mobile phones are now covered by the European Union Nickel Directive. *Contact Dermatitis* 61, 56–57.

- (25) Shah, M., Lewis, F. M., and Gawkrödger, D. J. (1998) Nickel as an occupational allergen. A survey of 368 nickel-sensitive subjects. *Arch. Dermatol.* 134 (10), 1231–1236.
- (26) Kiec-Swierczynska, M. (1996) Occupational allergic contact dermatitis in Lodz: 1990–1994. *Occup. Med (London)* 46 (3), 205–208.
- (27) Shum, K. W., Meyer, J. D., Chen, Y., Cherry, N., and Gawkrödger, D. J. (2003) Occupational contact dermatitis to nickel: Experience of the British dermatologists (EPIDERM) and occupational physicians (OPRA) surveillance schemes. *Occup. Environ. Med.* 60 (12), 954–957.
- (28) Dickel, H., Kuss, O., Schmidt, A., and Diepgen, T. L. (2002) Occupational relevance of positive standard patch-test results in employed persons with an initial report of an occupational skin disease. *Int. Arch. Occup. Environ. Health* 75 (6), 423–434.
- (29) Thyssen, J. P., Milting, K., Bregno, A., Sosted, H., Johansen, J. D., and Menné T. Nickel allergy in patch tested female hairdressers and assessment of nickel release from hairdressers scissors and crochet hooks. *Contact Dermatitis*, in press.
- (30) Lidén, C., Skare, L., Nise, G., and Vahter, M. (2008) Deposition of nickel, chromium, and cobalt on the skin in some occupations—Assessment by acid wipe sampling. *Contact Dermatitis* 58 (6), 347–354.
- (31) Lidén, C., Rondell, E., Skare, L., and Nalbanti, A. (1998) Nickel release from tools on the Swedish market. *Contact Dermatitis* 39 (3), 127–131.
- (32) Wall, L. M., and Gebauer, K. A. (1991) Occupational skin disease in Western Australia. *Contact Dermatitis* 24 (2), 101–109.
- (33) Martial, R. (1908) La “Gâle” du ciment. *Presse Med.* 64, 507–508.
- (34) Menné, T., and Bachmann, E. (1979) Permanent disability from skin diseases. A study of 564 patients registered over a six year period. *Derm. Beruf. Umwelt.* 27 (2), 37–42.
- (35) Zachariae, C. O., Agner, T., and Menné, T. (1996) Chromium allergy in consecutive patients in a country where ferrous sulfate has been added to cement since 1981. *Contact Dermatitis* 35 (2), 83–85.
- (36) Avnstorp, C. (1989) Follow-up of workers from the prefabricated concrete industry after the addition of ferrous sulphate to Danish cement. *Contact Dermatitis* 20 (5), 365–371.
- (37) Cheng, T. Y., Tseng, Y. H., Sun, C. C., and Chu, C. Y. (2008) Contact sensitization to metals in Taiwan. *Contact Dermatitis* 59 (6), 353–360.
- (38) Chou, T. C., Chang, H. Y., Chen, C. J., Yu, H. S., Wu, J. D., Sheu, S. C., and Shih, T. S. (2008) Effect of hand dermatitis on the total body burden of chromium after ferrous sulfate application in cement among cement workers. *Contact Dermatitis* 59 (3), 151–156.
- (39) Skoet, R., Olsen, J., Mathiesen, B., Iversen, L., Johansen, J. D., and Agner, T. (2004) A survey of occupational hand eczema in Denmark. *Contact Dermatitis* 51 (4), 159–166.
- (40) Athavale, P., Shum, K. W., Chen, Y., Agius, R., Cherry, N., and Gawkrödger, D. J. (2007) Occupational dermatitis related to chromium and cobalt: experience of dermatologists (EPIDERM) and occupational physicians (OPRA) in the U.K. over an 11-year period (1993–2004). *Br. J. Dermatol.* 157 (3), 518–522.
- (41) Geier, J., Lessmann, H., Hellweg, B., Jappe, U., Spornraft-Ragaller, P., Fuchs, T., Aberer, W., Frosch, P. J., Weisshaar, E., Mahler, V., Löffler, H., Skudlik, C., Szliska, C., Koch, P., Pfohler, C., Lilie, M., Becker, D., Trcka, J., Meyer, J., Hahn, J. U., and Adam, M. (2009) Chromated metal products may be hazardous to patients with chromate allergy. *Contact Dermatitis* 60 (4), 199–202.
- (42) Thyssen, J. P., Jensen, P., Carlsen, B. C., Engkilde, K., Menné, T., and Johansen, J. D. The prevalence of chromium allergy in Denmark is currently increasing as a result of leather exposure. *Br. J. Dermatol.*, in press.
- (43) Aslan, A. (2009) Determination of heavy metal toxicity of finished leather solid waste. *Bull. Environ. Contam. Toxicol.* 82, 633–638.
- (44) Rydin, S. (2002) Investigation of the content of CrVI and CrIII in leather products on the Danish market (Danish Environmental Protection Agency, Ed.)
- (45) Freeman, S. (1997) Shoe dermatitis. *Contact Dermatitis* 36 (5), 247–251.
- (46) Geier, J., Schnuch, A., and Frosch, P. J. (2000) Contact allergy to dichromate in women. *Dermatol. Beruf. Umwelt* 48, 4–10.
- (47) Hansen, M. B., Menné, T., and Johansen, J. D. (2006) Cr(III) and Cr(VI) in leather and elicitation of eczema. *Contact Dermatitis* 54 (5), 278–282.
- (48) Shackelford, K. E., and Belsito, D. V. (2002) The etiology of allergic-appearing foot dermatitis: A 5-year retrospective study. *J. Am. Acad. Dermatol.* 47 (5), 715–721.
- (49) Lidén, C., Bruze, M., and Menné, T. (2006) Metals. In *Contact Dermatitis* (Frosch, P. J., Menné, T., and Lepoittevin, J.-P., Eds.) pp 537–568. Springer, Berlin, Heidelberg, New York.
- (50) Nielsen, N. H., and Menné, T. (1992) Allergic contact sensitization in an unselected Danish population. The Glostrup Allergy Study, Denmark. *Acta Derm.-Venereol.* 72 (6), 456–460.
- (51) Meijer, C., Bredberg, M., Fischer, T., and Widstrom, L. (1995) Ear piercing, and nickel and cobalt sensitization, in 520 young Swedish men doing compulsory military service. *Contact Dermatitis* 32 (3), 147–149.
- (52) Lidén, C., and Wahlberg, J. E. (1994) Cross-reactivity to metal compounds studied in guinea pigs induced with chromate or cobalt. *Acta Derm.-Venereol.* 74 (5), 341–343.
- (53) Wahlberg, J. E., and Lidén, C. (2000) Cross-reactivity patterns of cobalt and nickel studied with repeated open applications (ROATS) to the skin of guinea pigs. *Am. J. Contact Dermatitis* 11 (1), 42–48.
- (54) Ruff, C. A., and Belsito, D. V. (2006) The impact of various patient factors on contact allergy to nickel, cobalt, and chromate. *J. Am. Acad. Dermatol.* 55 (1), 32–39.
- (55) Rystedt, I., and Fischer, T. (1983) Relationship between nickel and cobalt sensitization in hard metal workers. *Contact Dermatitis* 9 (3), 195–200.
- (56) Vilaplana, J., Grimalt, F., Romaguera, C., and Mascaro, J. M. (1987) Cobalt content of household cleaning products. *Contact Dermatitis* 16 (3), 139–141.
- (57) Basketter, D. A., Briatico-Vangosa, G., Kaestner, W., Lally, C., and Bontinck, W. J. (1993) Nickel, cobalt and chromium in consumer products: A role in allergic contact dermatitis? *Contact Dermatitis* 28 (1), 15–25.
- (58) Basketter, D. A., Angelini, G., Ingber, A., Kern, P. S., and Menné, T. (2003) Nickel, chromium and cobalt in consumer products: Revisiting safe levels in the new millennium. *Contact Dermatitis* 49 (1), 1–7.
- (59) Hosoki, M., Bando, E., Asaoka, K., Takeuchi, H., and Nishigawa, K. (2009) Assessment of allergic hypersensitivity to dental materials. *Biomed. Mater. Eng.* 19 (1), 53–61.
- (60) Rystedt, I. (1979) Evaluation and relevance of isolated test reactions to cobalt. *Contact Dermatitis* 5 (4), 233–238.
- (61) Fischer, T., and Rystedt, I. (1983) Cobalt allergy in hard metal workers. *Contact Dermatitis* 9 (2), 115–121.
- (62) Ekqvist, S., Svedman, C., Moller, H., Kehler, M., Pripp, C. M., Bjork, J., Gruvberger, B., Holmstrom, E., Gustavsson, C. G., and Bruze, M. (2007) High frequency of contact allergy to gold in patients with endovascular coronary stents. *Br. J. Dermatol.* 157 (4), 730–738.
- (63) Netterlid, E., Hindsen, M., Bjork, J., Ekqvist, S., Guner, N., Henricson, K. A., and Bruze, M. (2009) There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. *Contact Dermatitis* 60 (1), 41–49.
- (64) Hostynek, J. J. (2003) Factors determining percutaneous metal absorption. *Food Chem. Toxicol.* 41 (3), 327–345.
- (65) Larese, F., Gianpietro, A., Venier, M., Maina, G., and Renzi, N. (2007) In vitro percutaneous absorption of metal compounds. *Toxicol. Lett.* 170 (1), 49–56.
- (66) Hostynek, J. J., Dreher, F., Nakada, T., Schwindt, D., Anigbogu, A., and Maibach, H. I. (2001) Human stratum corneum adsorption of nickel salts. Investigation of depth profiles by tape stripping in vivo. *Acta Derm.-Venereol. Suppl. (Stockholm)* 212, 11–18.
- (67) Hostynek, J. J., Dreher, F., Pelosi, A., Anigbogu, A., and Maibach, H. I. (2001) Human stratum corneum penetration by nickel. In vivo study of depth distribution after occlusive application of the metal as powder. *Acta Derm.-Venereol. Suppl. (Stockholm)* 212, 5–10.
- (68) Fullerton, A., and Hoelgaard, A. (1988) Binding of nickel to human epidermis in vitro. *Br. J. Dermatol.* 119 (5), 675–682.
- (69) Fullerton, A., Andersen, J. R., and Hoelgaard, A. (1988) Permeation of nickel through human skin in vitro—Effect of vehicles. *Br. J. Dermatol.* 118 (4), 509–516.
- (70) Gammelgaard, B., Fullerton, A., Avnstorp, C., and Menné, T. (1992) Permeation of chromium salts through human skin in vitro. *Contact Dermatitis* 27 (5), 302–310.
- (71) Samitz, M. H., and Katz, S. (1964) A study of the chemical reactions between chromium and skin. *J. Invest. Dermatol.* 42, 35–43.
- (72) Scansetti, G., Botta, G. C., Spinelli, P., Reviglione, L., and Ponzetti, C. (1994) Absorption and excretion of cobalt in the hard metal industry. *Sci. Total Environ.* 150 (1–3), 141–144.
- (73) Larese, F. F., Maina, G., Adams, G., Venier, M., Coceani, N., Bussani, R., Massiccio, M., Barbieri, P., and Spinelli, P. (2004) In vitro percutaneous absorption of cobalt. *Int. Arch. Occup. Environ. Health* 77 (2), 85–89.
- (74) Allenby, C. F., and Goodwin, B. F. (1983) Influence of detergent washing powders on minimal eliciting patch test concentrations of nickel and chromium. *Contact Dermatitis* 9 (6), 491–499.
- (75) Allenby, C. F., and Basketter, D. A. (1994) The effect of repeated open exposure to low levels of nickel on compromised hand skin of nickel-allergic subjects. *Contact Dermatitis* 30 (3), 135–138.
- (76) Nielsen, N. H., Menné, T., Kristiansen, J., Christensen, J. M., Borg, L., and Poulsen, L. K. (1999) Effects of repeated skin exposure to low nickel concentrations: a model for allergic contact dermatitis to nickel on the hands. *Br. J. Dermatol.* 141 (4), 676–682.

- (77) Nielsen, N. H., Kristiansen, J., Borg, L., Christensen, J. M., Poulsen, L. K., and Menné, T. (2000) Repeated exposures to cobalt or chromate on the hands of patients with hand eczema and contact allergy to that metal. *Contact Dermatitis* 43 (4), 212–215.
- (78) Filon, F. L., D'Agostin, F., Crosera, M., Adami, G., Bovenzi, M., and Maina, G. (2009) In vitro absorption of metal powders through intact and damaged human skin. *Toxicol. In Vitro* 23 (4), 574–579.
- (79) Cavani, A., De, P. O., and Girolomoni, G. (2007) New aspects of the molecular basis of contact allergy. *Curr. Opin. Allergy Clin. Immunol.* 7 (5), 404–408.
- (80) Lepoittevin, J.-P. (2006) Molecular aspects of allergic contact dermatitis. In *Contact Dermatitis* (Frosch, P. J., Menné, T., and Lepoittevin, J.-P., Eds.) pp 45–68, Springer, Berlin.
- (81) Gernerding, K., Moulon, C., Karp, D. R., Van, B. J., Koning, F., Wild, D., Pflugfelder, U., and Weltzien, H. U. (2003) A new type of metal recognition by human T cells: contact residues for peptide-independent bridging of T cell receptor and major histocompatibility complex by nickel. *J. Exp. Med.* 197 (10), 1345–1353.
- (82) Schram, S. E., and Warshaw, E. M. (2007) Genetics of nickel allergic contact dermatitis. *Dermatitis* 18 (3), 125–133.
- (83) Bryld, L. E., Hindsberger, C., Kyvik, K. O., Agner, T., and Menné, T. (2004) Genetic factors in nickel allergy evaluated in a population-based female twin sample. *J. Invest. Dermatol.* 123 (6), 1025–1029.
- (84) Novak, N., Baurecht, H., Schafer, T., Rodriguez, E., Wagenpfeil, S., Klopp, N., Heinrich, J., Behrendt, H., Ring, J., Wichmann, E., Illig, T., and Weidinger, S. (2008) Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J. Invest. Dermatol.* 128, 1430–1435.
- (85) Candi, E., Schmidt, R., and Melino, G. (2005) The cornified envelope: a model of cell death in the skin. *Nat. Rev. Mol. Cell Biol.* 6 (4), 328–340.
- (86) Weidinger, S., Illig, T., Baurecht, H., Irvine, A. D., Rodriguez, E., az-Lacava, A., Klopp, N., Wagenpfeil, S., Zhao, Y., Liao, H., Lee, S. P., Palmer, C. N., Jenneck, C., Maintz, L., Hagemann, T., Behrendt, H., Ring, J., Nothen, M. M., McLean, W. H., and Novak, N. (2006) Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J. Allergy Clin. Immunol.* 118 (1), 214–219.
- (87) McGrath, J. A., and Uitto, J. (2008) The filaggrin story: Novel insights into skin-barrier function and disease. *Trends Mol. Med.* 14 (1), 20–27.
- (88) Thyssen, J. P., Carlsen, B. C., and Menné, T. (2008) Nickel sensitization, hand eczema, and loss-of-function mutations in the filaggrin gene. *Dermatitis* 19 (6), 303–307.
- (89) Peltonen, L., and Fraki, J. (1983) Prevalence of dichromate sensitivity. *Contact Dermatitis* 9 (3), 190–194.
- (90) Dotterud, L. K., and Smith-Sivertsen, T. (2007) Allergic contact sensitization in the general adult population: A population-based study from Northern Norway. *Contact Dermatitis* 56 (1), 10–15.
- (91) Schafer, T., Bohler, E., Ruhdorfer, S., Weigl, L., Wessner, D., Filipiak, B., Wichmann, H. E., and Ring, J. (2001) Epidemiology of contact allergy in adults. *Allergy* 56 (12), 1192–1196.
- (92) White, J. M., Gilmour, N. J., Jeffries, D., Duangdeedee, I., Kullavanijaya, P., Basketter, D. A., and McFadden, J. P. (2007) A general population from Thailand: Incidence of common allergens with emphasis on para-phenylenediamine. *Clin. Exp. Allergy* 37 (12), 1848–1853.
- (93) Nielsen, N. H., and Menné, T. (1993) Nickel sensitization and ear piercing in an unselected Danish population. Glostrup Allergy Study. *Contact Dermatitis* 29 (1), 16–21.
- (94) Thyssen, J. P., Linneberg, A., Menné, T., Nielsen, N. H., and Johansen, J. D. Contact allergy to allergens of the TRUE-test (panel 1 and 2) has decreased modestly in the general population. *Br. J. Dermatol.*, in press.
- (95) Thyssen, J. P., Johansen, J. D., Menné, T., Nielsen, N. H., and Linneberg, A. (2009) Nickel allergy in Danish women before and after nickel regulation. *N. Engl. J. Med.* 360 (21), 2259–2260.
- (96) ESSCA writing group (2009) The European baseline series in 10 European countries, 2005/2006—Results of the European Surveillance System of Contact Allergies (ESSCA). *Contact Dermatitis* 61, 31–38.
- (97) Bjorkner, B., Bruze, M., and Moller, H. (1994) High frequency of contact allergy to gold sodium thiosulfate. An indication of gold allergy? *Contact Dermatitis* 30 (3), 144–151.
- (98) Pratt, M. D., Belsito, D. V., DeLeo, V. A., Fowler, J. F., Jr., Fransway, A. F., Maibach, H. I., Marks, J. G., Mathias, C. G., Rietschel, R. L., Sasseville, D., Sherertz, E. F., Storrs, F. J., Taylor, J. S., and Zug, K. (2004) North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 15 (4), 176–183.
- (99) Ahlgren, C., Ahnlied, I., Bjorkner, B., Bruze, M., Liedholm, R., Moller, H., and Nilner, K. (2002) Contact allergy to gold is correlated to dental gold. *Acta Derm.-Venereol.* 82 (1), 41–44.
- (100) Aberer, W., Holub, H., Strohal, R., and Slavicek, R. (1993) Palladium in dental alloys—The dermatologists' responsibility to warn? *Contact Dermatitis* 28 (3), 163–165.
- (101) Bordel-Gomez, M. T., Miranda-Romero, A., and Castrodeza-Sanz, J. (2008) Isolated and concurrent prevalence of sensitization to transition metals in a Spanish population. *J. Eur. Acad. Dermatol. Venereol.* 22 (12), 1452–1457.
- (102) Bordel-Gomez, M. T., and Miranda-Romero, A. (2008) Palladium allergy: A frequent sensitisation. *Allergol. Immunopathol. (Madr.)* 36 (5), 306–307.
- (103) Kranke, B., and Aberer, W. (1996) Multiple sensitivities to metals. *Contact Dermatitis* 34 (3), 225.
- (104) Hemmer, W., Wantke, F., Focke, M., Gotz, M., and Jarisch, R. (1996) Evaluation of cutaneous hypersensitivity to aluminum by routine patch testing with AlCl₃(3). *Contact Dermatitis* 34 (3), 217–218.
- (105) Schnuch, A., and Uter, W. (2003) Decrease in nickel allergy in Germany and regulatory interventions. *Contact Dermatitis* 49 (2), 107–108.
- (106) Thyssen, J. P., Johansen, J. D., Carlsen, B. C., and Menné, T. (2009) Prevalence of nickel and cobalt allergy among female patients with dermatitis before and after Danish government regulation: A 23-year retrospective study. *J. Am. Acad. Dermatol.*, in press.
- (107) Rietschel, R. L., Fowler, J. F., Warshaw, E. M., Belsito, D., DeLeo, V. A., Maibach, H. I., Marks, J. G., Mathias, C. G., Pratt, M., Sasseville, D., Storrs, F. J., Taylor, J. S., and Zug, K. A. (2008) Detection of nickel sensitivity has increased in North American patch-test patients. *Dermatitis* 19 (1), 16–19.
- (108) Jacob, S. E., Moennich, J. N., McKean, B. A., Zirwas, M. J., and Taylor, J. S. (2009) Nickel allergy in the United States: A public health issue in need of a “nickel directive”. *J. Am. Acad. Dermatol.* 60, 1067–1069.
- (109) Hindsen, M., Persson, L., and Gruvberger, B. (2005) Allergic contact dermatitis from cobalt in jewellery. *Contact Dermatitis* 53 (6), 350–351.
- (110) Larese, F. F., Uderzo, D., and Bagnato, E. (2003) Sensitization to palladium chloride: a 10-year evaluation. *Am. J. Contact Dermatitis* 14 (2), 78–81.
- (111) Goon, A. T., and Goh, C. L. (2005) Metal allergy in Singapore. *Contact Dermatitis* 52 (3), 130–132.
- (112) Nguyen, S. H., and Maibach, H. (2008) Prevalence of patch test results from 1970 to 2002 in a multi-centre population in North America (NACDG). *Contact Dermatitis* 58 (2), 101–106.
- (113) Fischer, T., and Rystedt, I. (1985) False-positive, follicular and irritant patch test reactions to metal salts. *Contact Dermatitis* 12 (2), 93–98.
- (114) Julander, A., Hindsen, M., Skare, L., and Lidén, C. (2009) Cobalt-containing alloys and their ability to release cobalt and cause dermatitis. *Contact Dermatitis* 60 (3), 165–170.
- (115) Comaish, S. (1969) A case of contact hypersensitivity to metallic gold. *Arch. Dermatol.* 99 (6), 720–723.
- (116) Rytter, M., and Schubert, H. (1971) Gold allergy as a result of primary epicutaneous sensitization from a gold ring. *Dermatologica* 142 (4), 209–218.
- (117) Fleming, C., Burden, D., Fallowfield, M., and Lever, R. (1997) Lymphomatoid contact reaction to gold earrings. *Contact Dermatitis* 37 (6), 298–299.
- (118) Nedorost, S., and Wagman, A. (2005) Positive patch-test reactions to gold: Patients' perception of relevance and the role of titanium dioxide in cosmetics. *Dermatitis* 16 (2), 67–70.
- (119) Fowler, J. F., Jr. (1988) Allergic contact dermatitis to gold. *Arch. Dermatol.* 124 (2), 181–182.
- (120) Bruze, M., Edman, B., Bjorkner, B., and Moller, H. (1994) Clinical relevance of contact allergy to gold sodium thiosulfate. *J. Am. Acad. Dermatol.* 31 (4), 579–583.
- (121) Vamnes, J. S., Morken, T., Helland, S., and Gjerdet, N. R. (2000) Dental gold alloys and contact hypersensitivity. *Contact Dermatitis* 42 (3), 128–133.
- (122) Koch, P., and Bahmer, F. A. (1999) Oral lesions and symptoms related to metals used in dental restorations: A clinical, allergological, and histologic study. *J. Am. Acad. Dermatol.* 41 (3, Part 1), 422–430.
- (123) Hindsen, M., Spiren, A., and Bruze, M. (2005) Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. *Contact Dermatitis* 53 (1), 2–8.
- (124) Uter, W., Fuchs, T., Hausser, M., and Ippen, H. (1995) Patch test results with serial dilutions of nickel sulfate (with and without detergent), palladium chloride, and nickel and palladium metal plates. *Contact Dermatitis* 32 (3), 135–142.
- (125) Thijs, L., Deraedt, K., and Goossens, A. (2008) Granuloma possibly induced by palladium after ear piercing. *Dermatitis* 19 (5), E26–E29.
- (126) Rustemeyer, T., van Hoogstraten, I. M. W., von Blomberg, B. M. E., and Scheper, R. J. (2006) Mechanisms in allergic contact dermatitis. In *Contact Dermatitis* (Frosch, P. J., Menné, T., and Lepoittevin, J.-P., Eds.) pp 11–33, Springer, Heidelberg.

- (127) Nielsen, N. H., Linneberg, A., Menné, T., Madsen, F., Frolund, L., Dirksen, A., and Jorgensen, T. (2001) Persistence of contact allergy among Danish adults: An 8-year follow-up study. *Contact Dermatitis* 45 (6), 350–353.
- (128) Kligman, A. M. (1966) The identification of contact allergens by human assay. 3. The maximization test: A procedure for screening and rating contact sensitizers. *J. Invest. Dermatol.* 47 (5), 393–409.
- (129) Upadhye, M. R., and Maibach, H. I. (1992) Influence of area of application of allergen on sensitization in contact dermatitis. *Contact Dermatitis* 27 (5), 281–286.
- (130) Andersen, K. E., Johansen, J. D., Bruze, M., Frosch, P. J., Goossens, A., Lepoittevin, J. P., Rastogi, S., White, I., and Menné, T. (2001) The time-dose-response relationship for elicitation of contact dermatitis in isoeugenol allergic individuals. *Toxicol. Appl. Pharmacol.* 170 (3), 166–171.
- (131) Hotchkiss, S. A., Miller, J. M., and Caldwell, J. (1992) Percutaneous absorption of benzyl acetate through rat skin in vitro. 2. Effect of vehicle and occlusion. *Food Chem. Toxicol.* 30 (2), 145–153.
- (132) Hextall, J. M., Alagaratnam, N. J., Glendinning, A. K., Holloway, D. B., Blaikie, L., Basketter, D. A., and McFadden, J. P. (2002) Dose-time relationships for elicitation of contact allergy to para-phenylenediamine. *Contact Dermatitis* 47 (2), 96–99.
- (133) Agner, T., Johansen, J. D., Overgaard, L., Volund, A., Basketter, D., and Menné, T. (2002) Combined effects of irritants and allergens. Synergistic effects of nickel and sodium lauryl sulfate in nickel-sensitized individuals. *Contact Dermatitis* 47 (1), 21–26.
- (134) Halbert, A. R., Gebauer, K. A., and Wall, L. M. (1992) Prognosis of occupational chromate dermatitis. *Contact Dermatitis* 27 (4), 214–219.
- (135) Harrison, P. V. (1979) A postal survey of patients with nickel and chromate dermatitis. *Contact Dermatitis* 5 (4), 229–232.
- (136) Rosen, R. H., and Freeman, S. (1993) Prognosis of occupational contact dermatitis in New South Wales, Australia. *Contact Dermatitis* 29 (2), 88–93.
- (137) Kalimo, K., Lammintausta, K., Jalava, J., and Niskanen, T. (1997) Is it possible to improve the prognosis in nickel contact dermatitis? *Contact Dermatitis* 37 (3), 121–124.
- (138) Gawkrödger, D. J., Healy, J., and Howe, A. M. (1995) The prevention of nickel contact dermatitis. A review of the use of binding agents and barrier creams. *Contact Dermatitis* 32 (5), 257–265.
- (139) Wohrl, S., Kriechbaumer, N., Hemmer, W., Focke, M., Brannath, W., Gotz, M., and Jarisch, R. (2001) A cream containing the chelator DTPA (diethylenetriaminepenta-acetic acid) can prevent contact allergic reactions to metals. *Contact Dermatitis* 44 (4), 224–228.
- (140) Fullerton, A., and Menné, T. (1995) In vitro and in vivo evaluation of the effect of barrier gels in nickel contact allergy. *Contact Dermatitis* 32 (2), 100–106.
- (141) Memon, A. A., Molokhia, M. M., and Friedmann, P. S. (1994) The inhibitory effects of topical chelating agents and antioxidants on nickel-induced hypersensitivity reactions. *J. Am. Acad. Dermatol.* 30 (4), 560–565.
- (142) van Ketel, W. G., and Bruynzeel, D. P. (1984) Chelating effect of EDTA on nickel. *Contact Dermatitis* 11 (5), 311–314.
- (143) Kaaber, K., Menné, T., Veien, N., and Hougaard, P. (1983) Treatment of nickel dermatitis with Antabuse; a double blind study. *Contact Dermatitis* 9 (4), 297–299.
- (144) Kaaber, K., Menné, T., Tjell, J. C., and Veien, N. (1979) Antabuse treatment of nickel dermatitis. Chelation—A new principle in the treatment of nickel dermatitis. *Contact Dermatitis* 5 (4), 221–228.
- (145) Kauffman, R. E., Banner, W., Jr., Blumer, J. L., Gorman, R. L., Lambert, G. H., and Snodgrass, W. (1990) Clotquinol (iodochlorohydroxyquin, Vioform) and iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 86, 797–798.
- (146) Watzig, V. (1974) Experiences with an anion-exchange protective ointment for chromate eczema. *Dermatol. Monatsschr.* 160 (3), 233–237.
- (147) Moseley, J. C., and Allen, H. J., Jr. (1971) Polyurethane coating in the prevention of nickel dermatitis. *Arch. Dermatol.* 103 (1), 58–60.
- (148) Sprigle, A. M., Marks, J. G., Jr., and Anderson, B. E. (2008) Prevention of nickel release with barrier coatings. *Dermatitis* 19 (1), 28–31.
- (149) Fischer, L. A., Menné, T., and Johansen, J. D. (2005) Experimental nickel elicitation thresholds—A review focusing on occluded nickel exposure. *Contact Dermatitis* 52 (2), 57–64.
- (150) Fischer, L. A., Menné, T., and Johansen, J. D. (2007) Dose per unit area—A study of elicitation of nickel allergy. *Contact Dermatitis* 56 (5), 255–261.
- (151) Kosann, M. K., Brancaccio, R. R., Shupack, J. L., Franks, A. G., Jr., and Cohen, D. E. (1998) Six-hour versus 48-h patch testing with varying concentrations of potassium dichromate. *Am. J. Contact Dermatitis* 9 (2), 92–95.
- (152) Rudzki, E., Rebandel, P., and Karas, Z. (1997) Patch testing with lower concentrations of chromate and nickel. *Contact Dermatitis* 37 (1), 46.
- (153) Hansen, M. B., Rydin, S., Menné, T., and Duus, J. J. (2002) Quantitative aspects of contact allergy to chromium and exposure to chrome-tanned leather. *Contact Dermatitis* 47 (3), 127–134.
- (154) Piela, Z., and Kiec-Swierczynska, M. (1998) Skin reactivity in subjects sensitive to different concentrations of nickel, chromium and cobalt. *Med. Pr.* 49 (5), 457–463.
- (155) Allenby, C. F., and Basketter, D. A. (1989) Minimum eliciting patch test concentrations of cobalt. *Contact Dermatitis* 20 (3), 185–190.
- (156) Thyssen, J. P., and Maibach, H. I. (2008) Drug-elicited systemic allergic (contact) dermatitis—Update and possible pathomechanisms. *Contact Dermatitis* 59 (4), 195–202.
- (157) Jensen, C. S., Menné, T., Lisby, S., Kristiansen, J., and Veien, N. K. (2003) Experimental systemic contact dermatitis from nickel: a dose-response study. *Contact Dermatitis* 49 (3), 124–132.
- (158) Santucci, B., Cristaudo, A., Cannistraci, C., and Picardo, M. (1988) Nickel sensitivity: Effects of prolonged oral intake of the element. *Contact Dermatitis* 19 (3), 202–205.
- (159) Veien, N. K., Hattel, T., and Laurberg, G. (1993) Low nickel diet: an open, prospective trial. *J. Am. Acad. Dermatol.* 29 (6), 1002–1007.
- (160) Kaaber, K., and Veien, N. K. (1977) The significance of chromate ingestion in patients allergic to chromate. *Acta Derm.-Venereol.* 57 (4), 321–323.
- (161) Moller, H., Bjorkner, B., and Bruze, M. (1996) Clinical reactions to systemic provocation with gold sodium thiomalate in patients with contact allergy to gold. *Br. J. Dermatol.* 135 (3), 423–427.
- (162) Veien, N. K., Hattel, T., Justesen, O., and Norholm, A. (1987) Oral challenge with nickel and cobalt in patients with positive patch tests to nickel and/or cobalt. *Acta Derm.-Venereol.* 67 (4), 321–325.
- (163) Raison-Peyron, N., Guillard, O., Khalil, Z., Guilhou, J. J., and Guillot, B. (2005) Nickel-elicited systemic contact dermatitis from a peripheral intravenous catheter. *Contact Dermatitis* 53 (4), 222–225.
- (164) Hallab, N. J., Caicedo, M., Finnegan, A., and Jacobs, J. J. (2008) Th1 type lymphocyte reactivity to metals in patients with total hip arthroplasty. *J. Orthop. Surg.* 3, 6.
- (165) Merritt, K., and Rodrigo, J. J. (1996) Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. *Clin. Orthop. Relat. Res.* 326, 71–79.
- (166) Buchet, S., Blanc, D., Humbert, P., Girardin, P., Vigan, M., Anguenot, T., and Agache, P. (1992) Pacemaker dermatitis. *Contact Dermatitis* 26 (1), 46–47.
- (167) Rostoker, G., Robin, J., Binet, O., Blamoutier, J., Paupe, J., Lessana-Leibowitch, M., Bedouelle, J., Sonneck, J. M., Garrel, J. B., and Millet, P. (1987) Dermatitis due to orthopaedic implants. A review of the literature and report of three cases. *J. Bone Joint Surg. Am.* 69 (9), 1408–1412.
- (168) Caicedo, M. S., Desai, R., McAllister, K., Reddy, A., Jacobs, J. J., and Hallab, N. J. (2009) Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: A novel mechanism for implant debris reactivity. *J. Orthop. Res.* 27 (7), 847–854.
- (169) Iijima, R., Ikari, Y., Amiya, E., Tanimoto, S., Nakazawa, G., Kyono, H., Hatori, M., Miyazawa, A., Nakayama, T., Aoki, J., Nakajima, H., and Hara, K. (2005) The impact of metallic allergy on stent implantation: Metal allergy and recurrence of in-stent restenosis. *Int. J. Cardiol.* 104 (3), 319–325.
- (170) Koster, R., Vieluf, D., Kiehn, M., Sommerauer, M., Kahler, J., Baldus, S., Meinertz, T., and Hamm, C. W. (2000) Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 356 (9245), 1895–1897.
- (171) Saito, T., Hokimoto, S., Oshima, S., Noda, K., Kojyo, Y., and Matsunaga, K. (2009) Metal allergic reaction in chronic refractory in-stent restenosis. *Cardiovasc. Revasc. Med.* 10 (1), 17–22.
- (172) Hillen, U., Haude, M., Erbel, R., and Goos, M. (2002) Evaluation of metal allergies in patients with coronary stents. *Contact Dermatitis* 47 (6), 353–356.
- (173) Norgaz, T., Hobikoglu, G., Serdar, Z. A., Aksu, H., Alper, A. T., Ozer, O., and Narin, A. (2005) Is there a link between nickel allergy and coronary stent restenosis? *Tohoku J. Exp. Med.* 206 (3), 243–246.
- (174) Svedman, C., Ekqvist, S., Moller, H., Bjork, J., Pripp, C. M., Gruvberger, B., Holmstrom, E., Gustavsson, C. G., and Bruze, M. (2009) A correlation found between contact allergy to stent material and restenosis of the coronary arteries. *Contact Dermatitis* 60 (3), 158–164.
- (175) Kim, R. H., Dennis, D. A., and Carothers, J. T. (2008) Metal-on-metal total hip arthroplasty. *J. Arthroplasty* 23 (7 Suppl.), 44–46.
- (176) Jacobs, J. J., Urban, R. M., Hallab, N. J., Skipor, A. K., Fischer, A., and Wimmer, M. A. (2009) Metal-on-metal bearing surfaces. *J. Am. Acad. Orthop. Surg.* 17 (2), 69–76.

- (177) Back, D. L., Young, D. A., and Shimmin, A. J. (2005) How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? *Clin. Orthop. Relat. Res.* 438, 177–181.
- (178) Gleizes, V., Poupon, J., Lazennec, J. Y., Chamberlin, B., and Saillant, G. (1999) Value and limits of determining serum cobalt levels in patients with metal on metal articulating prostheses. *Rev. Chir. Orthop. Reparatrice Appar. Mot.* 85 (3), 217–225.
- (179) MacDonald, S. J., McCalden, R. W., Chess, D. G., Bourne, R. B., Rorabeck, C. H., Cleland, D., and Leung, F. (2003) Metal-on-metal versus polyethylene in hip arthroplasty: A randomized clinical trial. *Clin. Orthop. Relat. Res.* 406, 282–296.
- (180) Schaffer, A. W., Pilger, A., Engelhardt, C., Zweymueller, K., and Ruediger, H. W. (1999) Increased blood cobalt and chromium after total hip replacement. *J. Toxicol. Clin. Toxicol.* 37 (7), 839–844.
- (181) Hallab, N., Merritt, K., and Jacobs, J. J. (2001) Metal sensitivity in patients with orthopaedic implants. *J. Bone Joint Surg. Am.* 83A (3), 428–436.
- (182) Thomas, P., Braathen, L. R., Dorig, M., Aubock, J., Nestle, F., Werfel, T., and Willert, H. G. (2009) Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy* 64, 1157–1165.
- (183) Mikhael, M. M., Hanssen, A. D., and Sierra, R. J. (2009) Failure of metal-on-metal total hip arthroplasty mimicking hip infection. A report of two cases. *J. Bone Joint Surg. Am.* 91 (2), 443–446.
- (184) Pandit, H., Glyn-Jones, S., Lardy-Smith, P., Gundle, R., Whitwell, D., Gibbons, C. L., Ostlere, S., Athanasou, N., Gill, H. S., and Murray, D. W. (2008) Pseudotumours associated with metal-on-metal hip resurfacings. *J. Bone Joint Surg. Br.* 90 (7), 847–851.
- (185) Smith, E., Mehta, A. J., and Statham, B. N. (2009) Metal sensitivity to Elektra prostheses—Two cases from a metal on metal implant for hand joint replacement. *Contact Dermatitis* 60 (5), 298.
- (186) Dietrich, K. A., Mazoochian, F., Summer, B., Reinert, M., Ruzicka, T., and Thomas, P. (2009) Intolerance reactions to knee arthroplasty in patients with nickel/cobalt allergy and disappearance of symptoms after revision surgery with titanium-based endoprotheses. *J. Dtsch. Dermatol. Ges.* 7 (5), 410–413.
- (187) Thomas, P., Bandl, W. D., Maier, S., Summer, B., and Przybilla, B. (2006) Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness in vitro: Case report and review of the literature. *Contact Dermatitis* 55 (4), 199–202.

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