

Review

Systemic contact dermatitis

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Abstract

Systemic contact dermatitis is an inflammatory skin disease that may occur in persons with contact allergy when they are exposed to the hapten orally, transcutaneously, per rectum, intravesically, intravenously, or by inhalation. The most common causes of systemic contact dermatitis are drugs used both topically and systemically. Other causes are ubiquitously occurring haptens, such as the metals nickel, cobalt, gold, and chromate, and aromatic substances such as spices. Avoidance of the offending hapten is the most obvious treatment. For some haptens, such as nickel, diet treatment may be effective. Chelation therapy with disulfiram is another therapeutic option in nickel-allergic patients with systemic contact dermatitis. Hyposensitization therapy has been attempted with some success in systemic contact dermatitis caused by nickel and *Parthenium hysterophorus*.

Introduction

Systemic contact dermatitis is defined as dermatitis that may occur in contact-sensitized persons when they are exposed to the haptens systemically, i.e. orally, per rectum, intravesically, transcutaneously, intravenously, or by inhalation.

This type of dermatitis has been described sporadically in the dermatological literature, and it has been reviewed by several authors.¹⁻³ In the 1930s, patients were often treated with the same antibiotics both topically and orally. Patients who were contact-sensitized to topical sulfonamides often had widespread cutaneous reactions when sulfonamides were administered orally.⁴

In the 1950s, Calnan⁵ and also Marcussen⁶ expressed curiosity as to why, among large groups of nickel-allergic patients, there were some who exhibited eruptions on areas of the skin not obviously exposed to nickel. They used the term secondary eruptions. These were usually seen in skin folds and on the hands, and they speculated that hematogenous spread of nickel might cause these eruptions.

Drug reactions provide good evidence that systemic contact dermatitis is a specific immune reaction. Sensitization can be detected by patch testing. As most drugs require a prescription, systemic exposure can, therefore, be controlled.

There is a multitude of case reports on systemic contact dermatitis from drugs but only a few well-controlled studies.

Isaksson⁷ challenged 15 patients with positive patch tests to budesonide with the inhalation of 100 and 800 µg budesonide or a placebo in a prospective,

randomized trial. Four of the seven who were challenged with budesonide experienced reactivation of previously positive patch-test sites, as well as papular exanthema and/or a flare-up of previous dermatitis. None of the eight patients who received a placebo had any reactions.

Ten of 12 neomycin-sensitive patients who were challenged orally with neomycin had a reaction. Five had flares of their original dermatitis, and six had flares of previously positive patch-test sites. Three developed vesicular hand eczema for the first time.⁸ Neomycin is poorly absorbed from the gastrointestinal tract. Even so, severe systemic reactions may be seen when contact-sensitized persons ingest the medicament.

Table 1 lists some of the drugs that have been implicated as the cause of systemic contact dermatitis. There can be cross-reactions between some of the drugs, as for example between gentamycin and neomycin.⁹ It is curious that prednisone can cause systemic contact dermatitis when given orally.^{10,11} This was pointed out in a review by Thyssen and Maibach.¹²

If a drug given systemically is an important treatment of a serious disease, it should not at the same time be marketed in a topical preparation intended for application on the skin.

Only a minority of drug eruptions are systemic contact dermatitis. Patch testing is, therefore, not generally useful in detecting the cause of a drug eruption.^{13,14}

Plants that cause systemic contact dermatitis

Systemic contact dermatitis from plants has been seen following ingestion of various rhus preparations, e.g.

Table 1 Medicaments that may cause systemic contact dermatitis

Acetylsalicylic acid ¹³³
5-Aminosalicylic acid ¹³⁴
Amlexanox ¹³⁵
Butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) ⁹⁶
Codeine ¹³⁶
Diclofenac ¹³⁷
Erythromycin ¹³⁸
Hydroxyquinoline ⁸
8-Methoxypsoralen ¹³⁹
Nystatin ^{140,141}
Penicillin ¹⁴²
Phenobarbital ¹⁴³
Pseudoephedrine ^{144,145}
Resorcinol ¹⁴⁶
Tetraethylthiuram disulfide ¹⁴⁷
Vitamin C ¹⁴⁸
Vitamin B6 ¹⁴⁹
Neomycin ¹⁵⁰

poison ivy and poison oak. Attempts at oral hyposensitization to these plants have caused eruptions of systemic contact dermatitis and anal pruritus.^{15–20}

Plant products containing chemicals that are closely related to the allergens of poison ivy and poison oak may cause widespread dermatitis. An example is the shells of cashew nuts. A batch of cashew nuts contaminated by bits of shells caused systemic contact dermatitis in persons sensitive to poison ivy or poison oak.^{21,22} A fixed eruption has also been caused by cashew nuts.²³

Plants of the *compositae* family may also cause systemic contact dermatitis. Chamomile is used for both topical preparations and tea, and cases of systemic contact dermatitis following the drinking of chamomile tea and the ingestion of other *Composita*-containing products,^{24–26} as well as infusion of chrysanthemum and other *Asteraceae* plants²⁷, have been described.

After its spread throughout India, *P. hystrophorus* has caused massive problems with dermatitis among Indian farmers. Systemic contact dermatitis has been suspected, possibly caused by the inhalation of plant material.²⁸ Hyposensitization of the individual patient has been seen as a means of alleviating the problem.²⁸ Twenty parthenium-sensitive patients were hyposensitized orally with extracts of *P. hystrophorus*. Six patients had to give up the procedure due to aggravation of their dermatitis. These six had systemic contact dermatitis. Although the 14 patients who completed the study benefited from the hyposensitization procedure, the improvement appeared to be temporary.²⁹

Mak *et al.*³⁰ suggested that widespread use of chrysanthemum tea in Asia and a consequent development of tolerance to sesquiterpene lactones could be responsible

for a low rate of sensitivity to sesquiterpene lactones in Asia compared with Europe.

Balsam of Peru has for decades been used as a marker of fragrance sensitivity. In addition to fragrances, it contains substances that are present in spices and other aromatic substances used in foodstuffs.

Case histories of the eruption of dermatitis, in particular hand eczema following the ingestion of aromatic foods, prompted experimental oral challenge with balsam of Peru in patients with positive patch tests to balsam of Peru and/or the perfume mixture.

In the initial experiments, 10 of 17 patients reacted to balsam of Peru, while one reacted to a placebo.³¹ Diet trials were instituted, and a reduced intake of spice-containing foods proved helpful in approximately half of the patients who were placed on the diet. It was also shown, however, that the outcome of dietary exclusion of aromatic substances in food could not be predicted by oral challenge with balsam of Peru.³² In another study, significant improvement of their dermatitis was seen in about half of the patients who followed a low-balsam diet.³³ There are other reports of aggravation of dermatitis after the ingestion of substances that contain balsams and improvement after following a low-balsam diet.^{34–36} An example of systemic contact dermatitis from balsam of Peru is given in Figure 1.

Hausen³⁷ suspected that coniferyl benzoate is one of the compounds responsible for systemic reactions to balsam of Peru. Srivastava and Cohen³⁸ found coniferyl alcohol and cinnamic alcohol in several varieties of tomatoes.

Oral challenge with spices in patients sensitive to balsam of Peru reactivated vesicular hand eczema in eight of 22 of the patients. A placebo reaction was seen in one patient, and three patients reacted to both balsam of Peru and the placebo.³⁹

**Figure 1** Dermatitis between the breasts in a patient with systemic contact dermatitis to balsam of Peru

It has not been possible to identify specific spices or other aromatic substances as particularly frequent causes of systemic contact dermatitis in patients with contact allergy to balsam of Peru. Fourteen of 29 who experienced aggravation of their dermatitis after the ingestion of specific food items mentioned spices as a possible cause. Four suggested cinnamon, four curry, and three vanilla.⁴⁰ Among Salam and Fowler's patients, the most commonly implicated foods were tomatoes, citrus, and spices.³³ Niinimäki⁴¹ found reactions to cinnamon and clove among patients with positive patch tests to these two spices. Belsito summarized the studies of balsam of Peru allergy and diet.⁴²

Propolis contains balsam-like substances. Komericki and Kränke⁴³ described a case of systemic contact dermatitis from propolis and reviewed the literature. There are several cases of contact stomatitis caused by propolis described in the literature but few well-documented cases of systemic contact dermatitis.^{44,45}

Garlic intake has caused systemic contact dermatitis. In the case published by Pereira *et al.*,⁴⁶ the patient reacted to patch testing with 1% diallyl disulfide in petrolatum, while the patients of Burden *et al.*⁴⁷ reacted to patch testing with a 5% aqueous extract of garlic. The intake of mango and also shiitake mushrooms has caused widespread dermatitis in sensitized persons.^{48,49}

Metals

Most studies of systemic contact dermatitis caused by metals have focused on nickel-allergic patients, but a number of other metals have been implicated as the cause of systemic contact dermatitis. These metals are nickel, cobalt, chromium, mercury, gold, and aluminum.

Nickel

Experimental oral challenge with 2.5–5.6 mg elemental nickel (given as $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$) carried out in double-blind designs showed that the dermatitis of patients with certain morphologies of dermatitis can be reproduced in a dose-dependent manner. While only a minority will experience aggravation of their dermatitis after oral challenge with 0.5 mg nickel, most nickel-sensitive patients will react to the ingestion of 5.6 mg nickel.⁵⁰

Jensen *et al.*⁵¹ carried out a dose-response study of oral challenge with nickel in a double-blind, placebo-controlled design. Seven of 10 nickel-sensitive patients reacted to 4 mg nickel, or an amount that is well above the daily intake of nickel in most parts of the world. Four of 10 patients reacted to challenge with 1 mg/0.3 mg nickel. In the same study, one of 10 reacted to a placebo.

None of the 20 non-nickel-sensitive controls reacted to 4 mg nickel or to a placebo.

Studies of nickel-sensitive patients with recurrent, vesicular hand eczema illustrate that it is possible to reproduce the clinical problem of the patient in a controlled fashion. Flares of previously positive nickel patch tests following oral challenge with nickel indicate that the reaction is antigen specific. This has been tested by Christensen *et al.*⁵² who carried out oral challenge with nickel in patients who had a positive patch test to nickel and an irritant reaction to a patch test with benzalkonium chloride. Reactivation of the nickel patch-test site, but no reactivation of the irritant patch-test reaction, was seen after oral challenge with nickel. Nielsen *et al.*⁵³ showed that a diet deliberately high in nickel caused a flare of vesicular hand eczema in a group of nickel-sensitive women. Examples of systemic contact dermatitis caused by nickel are given in Figures 2–5.



Figure 2 Recurrent vesicular dermatitis of the fingers in a nickel-sensitive patient with systemic contact dermatitis



Figure 3 Vesicular eruption of the fingertips in a nickel-sensitive patient with systemic contact dermatitis



Figure 4 Dermatitis in the antecubital fossae in a nickel-sensitive patient with systemic contact dermatitis



Figure 5 Dermatitis in the axillae of a nickel-sensitive patient with systemic contact dermatitis

As the clinical problem of some nickel-allergic patients can be reproduced after oral challenge with nickel and a diet with a high nickel content, it is tempting to try to reduce the amount of nickel in the body. This can be done by following a low-nickel diet. Such diet trials have been published, and for selected nickel-sensitive patients an improvement of the nickel dermatitis has been seen for about half the patients during the diet period.^{54,55} Veien *et al.*⁵⁶ found that of all 770 nickel-sensitive patients seen in a private practice of dermatology over a period of

five years, 216 had morphologies of dermatitis consistent with systemic contact dermatitis (recurrent, vesicular hand eczema that persisted in spite of attempts to remove external contact with allergens and irritants, anogenital dermatitis, vasculitis-like lesions with no other obvious cause, and other clinical manifestations). Ninety of the patients who had a flare of their dermatitis after oral challenge with 2.5 mg nickel but not after a placebo were asked to follow a low-nickel diet for 1–2 months. For 58 of the patients, improvement was seen after 1–2 months. In response to a questionnaire sent to the patients 1–2 years later, 40 of the 55 who responded maintained that the diet was helpful. Other investigators have published similar results of diet trials.^{57,58}

Recent reports have shown that children may also have manifestations of nickel and cobalt sensitivity that were seen to improve on a diet with a low content of these metals.^{59,60}

In a modified meta-analysis of selected studies of nickel-sensitive patients who had undergone oral challenge with nickel, Jensen *et al.*⁶¹ concluded that only a minority of nickel-sensitive patients can be expected to develop systemic contact dermatitis from the amounts of nickel normally present in the diet (0.22–0.35 mg nickel). This range of intake may underestimate the maximum intake of nickel, estimated to be up to 500–1000 µg nickel per day in 4- to 7-year-old children in Germany.⁶²

The oral intake of metals may be higher than suspected due to the presence of nickel in some complementary and alternative remedies and chromium in a nutritional supplement.^{63,64}

Chelation is another means of reducing the amount of nickel in the body. Disulfiram has been shown to chelate nickel, and controlled treatment trials with disulfiram in nickel-sensitive patients have been successful.^{65–67} The combination of 125–250 mg disulfiram and a low-nickel diet was used in a study of 11 patients with nickel allergy and vesicular hand eczema. Ten controls with nickel allergy and vesicular hand eczema continued the intake of their normal diet and were given a placebo tablet every day. The hand eczema of 10 of the 11 patients in the intervention group healed, compared with one of 10 in the control group.⁶⁸

Immune modulation is a third way of treating patients with nickel sensitivity and systemic contact dermatitis. If nickel is given orally to mice before an attempt is made to cutaneously sensitize the mice, the mice are difficult to sensitize. If nickel is given orally to already sensitized mice, a flare-up reaction is seen.⁶⁹ Similarly, fewer young girls become nickel-sensitive if they have worn orthodontic metal braces before they have their ears pierced than if piercing precedes the orthodontic procedure.^{70,71}

It appears from the above that it is possible to interfere with sensitization to nickel. Attempts have also been made to “hyposensitize” already sensitized persons. An oral or sublingual dose of nickel, usually starting with a low dose that is gradually increased, has shown promising results in the suppression of clinical signs of nickel dermatitis.^{72–76}

In studies with mice, it has recently been suggested that biotin supplementation may inhibit upregulation of IL-1 beta and that this may help control reactions to nickel in nickel-sensitive patients.⁷⁷

Cobalt

Cobalt sensitivity is often associated with nickel sensitivity. A positive patch test to cobalt without concomitant nickel allergy is unusual. For some cobalt-sensitive persons, it is possible to reactivate previous dermatitis after oral challenge with cobalt. Six of nine cobalt-sensitive patients reacted to oral challenge with 1 mg cobalt in a placebo-controlled design. Most of the patients had vesicular hand eczema.⁷⁸ In addition to vesicular hand eczema, the clinical features associated with systemic cobalt dermatitis include stomatitis⁷⁹ and widespread dermatitis. Figure 6 shows eyelid dermatitis in a cobalt-sensitive patient with systemic contact dermatitis. Stuckert and Nedorost⁸⁰ have made suggestions for a low-cobalt diet.

Chromate

Chromium is an inert metal, while chromium salts, particularly hexavalent chromate, are a common sensitizer.

The use of ferrous sulfate to reduce the hexavalent chromate in cement to trivalent chromate has reduced the incidence of severe hand dermatitis characteristically seen in masons.

Systemic contact dermatitis in chromate-sensitive patients has been linked to recurrent, vesicular hand

eczema.^{81,82} In two double-blind studies, a total of 61 patients were challenged orally with 2.5 mg chromium in a double-blind, placebo-controlled fashion. Twenty-eight of the patients had a flare-up of their dermatitis after challenge with chromate but not the placebo. The majority of the patients had vesicular hand eczema. Therapeutic options such as a low-chromate diet have been reviewed by Sharma.⁸³

Mercury

Mercury salts have been linked to systemic contact dermatitis – most often in connection with exposure to mercury evaporated from broken thermometers. The primary sensitization has often been caused by amalgam and, clinically, lichenoid streaks are seen on the buccal mucosa adjacent to amalgam dental fillings. Widespread rashes have been seen when persons sensitized to mercury are exposed to mercury vapors.^{84,85}

Gold

Gold is a very stable metal. While sensitization does occur, there are few examples of classical contact dermatitis at cutaneous sites of contact with high-carat gold. Lichenoid eruptions on the gingiva and buccal mucosa at sites of contact with gold fillings are the most common clinical manifestation of gold contact stomatitis.

Controlled challenge experiments have shown that the injection of gold salts in gold-sensitized persons can cause widespread dermatitis similar to the eruptions seen in mercury-sensitive persons. The eruptions differ from the reactivation of vesicular hand eczema seen in nickel-sensitive patients following oral challenge with nickel.^{86,87}

There is a statistical correlation between gold allergy and the presence of dental gold.^{88,89} There is also a correlation between gold allergy and the presence of gold-plated stents for coronary arteries, as well as for the risk of restenosis.^{90–92} The importance of patch testing with gold has been addressed in a review by Möller.⁸⁸

Other substances that can cause systemic contact dermatitis

Paraben-sensitive patients have been shown to react to oral challenge with methyl peroxybenzoate or with a mixture of different parabens.^{93,94} Veien *et al.*⁹⁵ challenged 14 paraben-sensitive patients orally with 220 mg methyl and propyl *p*-hydroxybenzoate in a double-blind, placebo-controlled design. Two of the patients had flares of their vesicular hand eczema after challenge with parabens but not the placebo.



Figure 6 Eyelid dermatitis in a cobalt-sensitive patient with systemic contact dermatitis

Butylhydroxyanisole and butylhydroxytoluene have been implicated as the cause of systemic contact dermatitis,⁹⁶ as have sorbic acid,⁹⁷ propylene glycol⁹⁸, and formaldehyde⁹⁹ (Table 1).

Systemic contact dermatitis from items within the body

The increasing use of joint replacement, cements used in these operations, metal screws and plates to stabilize fractures, pacemakers, metal stents, plastic and metal tooth repair, dentures, artificial heart valves, in-dwelling catheters, and plastics used to repair hernias all increase the risk of sensitization to the materials in these foreign bodies. In spite of this, allergic contact dermatitis from foreign objects in the body is rarely reported. This may, in part, be because the foreign bodies have no contact with the skin where sensitization usually takes place.

The oral cavity

Orthodontic treatment with metal wires and metals in dental prostheses have been shown to cause systemic contact dermatitis due to the content of nickel, cobalt, and chromium in the wires.^{100–103}

Surprisingly, very little has been reported about contact stomatitis from acrylate-based dental restorations.¹⁰⁴

Joint replacement

Metal-on-plastic or ceramic joint replacements have been used for many years. Second generation metal-on-metal prostheses are longer lasting, but erosion and the release of minute metal particles do occur.

Generally speaking, joint replacement does not lead to contact allergy to the materials used in the prostheses.

Thyssen *et al.*¹⁰⁵ performed a case-control study of total hip arthroplasty and found no increased risk of surgical revision in patients with metal allergies, nor was there an increased risk of metal allergy in these patients.

There are, however, reports of the loosening of prostheses after the increased use of metal-to-metal hip prostheses.¹⁰⁶ Lymphocyte proliferation assays showed increased reactivity to nickel and cobalt among patients with metal-on-metal prostheses.¹⁰⁷

It has been suggested that metal-induced lymphocyte proliferation may contribute to osteoclastogenesis seen in the aseptic loosening of prostheses.¹⁰⁸ It is possible that this type of reactivity is best diagnosed by means of lymphocyte proliferation assays.¹⁰⁹

Allergic contact dermatitis to the cements used to secure prostheses is rare. Thomas *et al.*¹¹⁰ found contact allergy to components of bone cement in 25% of 113 patients

with cemented prostheses, but not all the reactions were clinically relevant. Haddad *et al.*¹¹¹ found seven patients with positive patch tests to *N,N*-dimethyl-para-toluidine, an accelerator used in bone cement. This reaction correlated with aseptic loosening of hip replacements.

Case reports have shown that nickel in spongiosa screws,¹¹² in a sacral stimulator,¹¹³ in catheters for intravenous infusions, and in an eyelet in an intravenous catheter^{114,115} may have caused systemic contact dermatitis.

The symptoms of a patient with widespread dermatitis and a strongly positive patch test to chromate disappeared after the removal of a knee prosthesis containing chromium.¹¹⁶

The relief of symptoms of dermatitis after the insertion of titanium-based prostheses in four patients with nickel/cobalt allergy speaks in favor of an association between metal allergy and arthroplasty materials.¹¹⁷

Thyssen *et al.*¹¹⁸ have provided advice as to the evaluation of patients with suspected allergic reactions to metals in implant material prior to the insertion of orthopedic implants as well as about patients who have already had implant surgery with complications. They suggest that clinicians should refrain from routine patch testing prior to surgery unless the patient has experienced complications suspected to be caused by allergy in connection with previous implant surgery or a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or healthcare provider.

A joint statement of relevant specialties in Germany recommended the use of titanium-based osteosynthesis materials in metal-allergic patients.¹¹⁹

The mechanism of systemic contact dermatitis

The reactivation of previously positive nickel patch-test sites after oral challenge with nickel but no reactivation of irritant patch tests induced by benzalkonium chloride indicates an antigen-specific, T-cell-mediated immune reaction. Likewise, the flare-up of previous nickel dermatitis after oral challenge with nickel indicates an immunologically specific reaction.^{52,120}

The baboon syndrome and reactivation of recurrent vesicular hand dermatitis may have other mechanisms in addition to specific immune reactions. Urticaria has been associated with positive patch tests to, for example, nickel,¹²¹ but this association is controversial.¹²² Systemic contact dermatitis caused by drugs has been reviewed by Thyssen and Maibach.¹² They suggest that mechanisms other than the classical delayed-type hypersensitivity may be operative.

A reduction in the peripheral blood of CD4⁺ cells, CD45⁺RO⁺ CD8⁺ cells were seen after oral challenge

with nickel in nickel-sensitive patients. The oral challenge induced maturation of naive T-cells into memory cells that accumulated in the intestinal mucosa.¹²³

Jensen *et al.*¹²⁴ studied skin-homing T-lymphocytes in the peripheral blood of nickel-sensitive women before and after oral challenge with nickel. CLA⁺CD45⁺Ro⁺CD8⁺ cells were significantly reduced in the peripheral blood after oral challenge with nickel. The cells were presumably effector cells that had travelled to the skin.

A significant IL-17 expression to nickel was seen in five patients with arthroplasty-associated complications. This expression was not seen in five patients without complications to the arthroplasty.¹²⁵

It is not clear whether adverse reactions to the materials used for arthroplasty are due to classical metal sensitivity that can be demonstrated by patch testing or whether more complex mechanisms are responsible.^{126–129}

In studies of inflammatory reactions in tissue around prostheses, it has been suggested that mechanisms other than cellular immune reactions may be operative. It is not clear whether sensitization to metals can occur without skin contact to the metal in question. Other examples are given in the section on joint replacement.

A woman with no history of metal allergy developed dermatitis overlying osteosynthesis material on the lower leg. The dermatitis improved after removal of the osteosynthesis material, but bouts of dermatitis recurred at the site of the operation. This was assumed to be due to a broken drill left at the fracture site. During the course of the skin disease, this patient also developed clinical evidence of metal sensitivity.¹³⁰

Averbeck *et al.*¹¹² suggested that patch tests might be false-negative if the implant material is located some distance from the skin. A biopsy of peri-implant tissue followed by a study of the T-cell infiltrate may be necessary in order to diagnose sensitivity to the implant material.

A patient with hand eczema had delayed healing of a fracture that had been repaired with titanium osteosynthesis material. A patch test to titanium was negative, but there was a specific proliferative response to titanium in a lymphocyte transformation test. All symptoms cleared after removal of the titanium osteosynthesis material.¹³¹

The issue of test methods used to identify metal sensitivity to implanted metal is further complicated by the possible development of tolerance in the individual person. It has been suggested that the concept of tolerance to contact allergens may be more common than previously thought.¹³²

Adverse reaction to implant materials is rare. Should such a reaction occur, most authors recommend the use of titanium osteosynthesis material.

In conclusion, although systemic contact dermatitis is a clinical entity, it is rare compared with allergic contact dermatitis elicited by cutaneous contact with the hapten.

Questions (Each question may have one or two correct answers – see answers on page 1456)

1. Which of the following drugs have caused systemic contact dermatitis?
 - a. Sulfonamide
 - b. Neomycin
 - c. Vitamin B₆
 - d. Hydroxyquinolines
 - e. All of the above
2. Can prednisone cause systemic contact dermatitis?
 - a. Yes
 - b. No
3. Chamomile tea has been described as a cause of systemic contact dermatitis.
 - a. Yes
 - b. No
4. Hyposensitization of already sensitized persons has been more or less successful for which of the following?
 - a. Poison ivy/poison oak
 - b. Nickel
 - c. Arnica montana
 - d. Dandelion
5. What is the most likely mechanism of systemic contact dermatitis?
 - a. An immediate-type immune reaction
 - b. Non-immunological mechanisms
 - c. A cellular immune reaction
 - d. Unknown
6. Which chemical compound is most likely to be involved in systemic contact dermatitis to balsam of Peru?
 - a. Oak moss
 - b. Musk-ambrette
 - c. Propolis
 - d. Coniferyl benzoate
7. Systemic contact dermatitis has been caused by which of the following metals?
 - a. Gold
 - b. Silver
 - c. Iron
 - d. Cobalt

8. What oral dose of nickel will cause a flare-up reaction in most nickel-sensitive persons?
 - a. 1 µg
 - b. 5 µg
 - c. 1 mg
 - d. 5 mg
9. Which clinical manifestations have, in particular, been linked to systemic contact dermatitis in nickel-sensitive patients?
 - a. Cheilitis
 - b. Anal pruritus
 - c. Recurrent vesicular hand eczema
 - d. Allergic vasculitis
10. Sensitization to nickel can be modulated by
 - a. Giving an oral dose of nickel prior to an attempt to sensitize
 - b. Giving an oral dose of nickel after an attempt to sensitize
 - c. An intramuscular injection of nickel prior to an attempt to sensitize
 - d. An intramuscular injection of nickel after an attempt to sensitize

References

- 1 Nijhawan RI, Molenda M, Zirwas MJ, *et al.* Systemic contact dermatitis. *Dermatol Clin* 2009; **27**: 355–364.
- 2 Jacob SE, Zapolanski T. Systemic contact dermatitis. *Dermatitis* 2008; **19**: 9–15.
- 3 Veien NK, Menné T. Systemic contact dermatitis. In: Johansen JD, Frosch PJ, Lepoittevin J-P, eds. *Contact Dermatitis*, 5th edn. Berlin: Springer, 2011: 347–360.
- 4 Park RG. Cutaneous hypersensitivity to sulphonamides. *Br Med J* 1943; **2**: 69–72.
- 5 Calnan CD. Nickel dermatitis. *Br J Derm* 1956; **68**: 229–236.
- 6 Marcussen PV. Spread of nickel dermatitis. *Dermatologica* 1957; **115**: 596–607.
- 7 Isaksson M. (2000) Clinical and experimental studies in corticosteroid contact allergy. Thesis, Department of Dermatology, University Hospital, Malmö, Sweden.
- 8 Ekelund A-G, Möller H. Oral provocation in eczematous contact allergy to neomycin and hydroxyquinolines. *Acta Dermatol Venerol (Stockh)* 1969; **49**: 422–426.
- 9 Ghadially R, Ramsay CA. Gentamicin: systemic exposure to a contact allergen. *J Am Acad Dermatol* 1988; **19**: 428–430.
- 10 Thong H-Y, Yokota M, Chan H, *et al.* Possible anergy after generalized orally elicited allergic contact dermatitis to corticosteroid. *Contact Derm* 2008; **58**: 126–128.
- 11 Isaksson M. Systemic contact allergy to corticosteroids revisited. *Contact Derm* 2007; **57**: 386–388.
- 12 Thyssen JP, Maibach HI. Drug-elicited systemic allergic (contact) dermatitis – update and possible pathomechanisms. *Contact Derm* 2008; **59**: 195–202.
- 13 Friedmann PS, Arden-Jones M. Patch testing in drug allergy. *Curr Opin Allergy Clin Immunol* 2010; **10**: 291–296.
- 14 Santiago F, Concalo M, Viera R, *et al.* Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). *Contact Derm* 2010; **62**: 47–53.
- 15 Kligman AM. Hyposensitization against *Rhus* dermatitis. *Arch Dermatol* 1958; **78**: 47–72.
- 16 Yoo KH, Seo SJ, Li K, *et al.* Ingestion of *Rhus* chicken causing systemic contact dermatitis in a Korean patient. *Clin Exp Dermatol* 2010; **35**: 756–758.
- 17 Werchniak AE, Schwarzenberger K. Poison ivy: an underreported cause of erythema multiforme. *J Am Acad Dermatol* 2004; **51**: S87–S88.
- 18 Park SD, Lee SW, Chun JH, *et al.* Clinical features of 31 patients with systemic contact dermatitis due to the ingestion of *Rhus* (lacquer). *Br J Dermatol* 2000; **142**: 937–942.
- 19 Oh S-H, Haw C-R, Lee M-H. Clinical and immunologic features of systemic contact dermatitis from ingestion of *Rhus* (*Toxicodendron*). *Contact Derm* 2003; **48**: 251–254.
- 20 Cardinali C, Francalanci S, Giomi B, *et al.* Systemic contact dermatitis from herbal and homeopathic preparations used for herpes virus treatment. *Acta Dermatol Venereol* 2004; **84**: 223–226.
- 21 Marks JG Jr, DeMelfi T, McCarthy MA, *et al.* Dermatitis from cashew nuts. *J Am Acad Dermatol* 1984; **10**: 627–631.
- 22 Hamilton TK, Zug KA. Systemic contact dermatitis to raw cashew nuts in a pesto sauce. *Am J Contact Dermatol* 1998; **9**: 51–54.
- 23 Fukushima S, Kidou M, Ihn H. Fixed food eruption caused by cashew nut. *Allergol Int* 2008; **57**: 285–287.
- 24 Cusack C, Buckley C. Compositae dermatitis in a herbal medicine enthusiast. *Contact Derm* 2005; **53**: 120–121.
- 25 Wintzen M, Donker AS, Van Zuuren EJ. Recalcitrant atopic dermatitis due to allergy to Compositae. *Contact Derm* 2003; **48**: 87–88.
- 26 Rycroft RJG. Recurrent facial dermatitis from chamomile tea. *Contact Derm* 2003; **48**: 229.
- 27 Lundh K, Hindsén M, Gruvberger B, *et al.* Contact allergy to herbal teas derived from Asteraceae plants. *Contact Derm* 2006; **54**: 196–201.
- 28 Mahajan VK, Sharma NL, Sharma RC. Parthenium dermatitis: is it a systemic contact dermatitis or an airborne contact dermatitis? *Contact Derm* 2004; **51**: 231–234.
- 29 Handa S, Sahoo B, Sharma VK. Oral hyposensitization in patients with contact dermatitis from *Parthenium hysterophorus*. *Contact Derm* 2001; **44**: 279–282.
- 30 Mak RK, White IR, White JM, *et al.* Lower incidence of sesquiterpene lactone sensitivity in a population in

- Asia versus a population in Europe: an effect of chrysanthemum tea? *Contact Derm* 2007; 57: 163–164.
- 31 Veien NK, Hattel T, Justesen O, *et al.* Oral challenge with balsam of Peru. *Contact Derm* 1985; 12: 104–107.
- 32 Veien NK, Hattel T, Laurberg G. Can oral challenge with balsam of Peru predict possible benefit from a low-balsam diet? *Am J Contact Derm* 1996; 7: 84–87.
- 33 Salam TN, Fowler JF Jr. Balsam-related systemic contact dermatitis. *J Am Acad Dermatol* 2001; 45: 377–381.
- 34 Pfützner W, Niedermeier A, Thomas P, *et al.* Systemic contact eczema against balsam of Peru. *J Dtsch Dermatol Ges* 2003; 1: 719–721.
- 35 Pfützner W, Thomas P, Niedermeier A, *et al.* Systemic contact dermatitis elicited by oral intake of balsam of Peru. *Acta Dermatol Venereol* 2003; 83: 294–295.
- 36 Doooms-Goossens A, Dubelloy R, Degreef H. Contact and systemic contact-type dermatitis to spices. *Dermatol Clin* 1990; 8: 89–93.
- 37 Hausen BM. Contact allergy to balsam of Peru. II. Patch test results in 102 patients with selected balsam of Peru constituents. *Am J Contact Derm* 2001; 12: 93–102.
- 38 Srivastava D, Cohen DE. Identification of the constituents of balsam of Peru in tomatoes. *Dermatitis* 2009; 20: 99–105.
- 39 Niinimäki A. Double-blind placebo-controlled peroral challenges in patients with delayed-type allergy to balsam of Peru. *Contact Derm* 1995; 33: 78–83.
- 40 Veien NK, Hattel T, Justesen O, *et al.* Reduction of intake of balsams in patients sensitive to balsam of Peru. *Contact Derm* 1985; 12: 270–273.
- 41 Niinimäki A. Delayed-type allergy to spices. *Contact Derm* 1984; 11: 34–40.
- 42 Belsito DV. Surviving on a balsam-restricted diet: cruel and unusual punishment or medically necessary therapy? *J Am Acad Dermatol* 2001; 45: 470–472.
- 43 Komericki P, Kränke B. Maculopapular exanthem from propolis: case report and review of systemic cutaneous and non-cutaneous reactions. *Contact Derm* 2009; 61: 353–355.
- 44 Walgrave SE, Warshaw EM, Glesne LA. Allergic contact dermatitis from Propolis. *Dermatitis* 2005; 16: 209–215.
- 45 Lee SY, Lee DR, You CE, *et al.* Autosensitization dermatitis associated with propolis-induced allergic contact dermatitis. *J Drugs Dermatol* 2006; 5: 458–460.
- 46 Pereira F, Hatia M, Cardoso J. Systemic contact dermatitis from diallyl disulfide. *Contact Derm* 2002; 46: 124.
- 47 Burden AD, Wilkinson SM, Beck MH, *et al.* Garlic-induced systemic contact dermatitis. *Contact Derm* 1994; 30: 299–325.
- 48 Thoo CHF, Freeman S. Hypersensitivity reaction to the ingestion of mango flesh. *Australas J Dermatol* 2008; 49: 116–119.
- 49 Kopp T, Mastan P, Mothes N, *et al.* Systemic allergic contact dermatitis due to consumption of raw shiitake mushroom. *Clin Exp Dermatol* 2009; 34: e910–e913.
- 50 Veien NK, Menné T, Maibach HI. Systemic contact dermatitis. In: Zhai H, Wilhelm K-P, Maibach HI, eds. *Marzulli and Maibach's Dermatotoxicology*, 7th edn. Boca Raton, FL: CRC Press, 2008: 144.
- 51 Jensen CS, Menné T, Lisby S, *et al.* Experimental systemic contact dermatitis from nickel: a dose-response study. *Contact Derm* 2003; 49: 124–132.
- 52 Christensen OB, Lindström C, Löfberg H, *et al.* Micro-morphology and specificity of orally induced flare-up reactions in nickel-sensitive patients. *Acta Dermatovenereol (Stockh)* 1981; 61: 505–510.
- 53 Nielsen GD, Jepsen LV, Jørgensen PJ, *et al.* Nickel-sensitive patients with vesicular hand eczema: oral challenge with a diet naturally high in nickel. *Br J Dermatol* 1990; 122: 299–308.
- 54 Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978; 98: 197–201.
- 55 Veien NK, Hattel T, Justesen O, *et al.* Dietary treatment of nickel dermatitis. *Acta Dermatol Venereol (Stockh)* 1985; 65: 138–142.
- 56 Veien NK, Hattel T, Laurberg G. Low nickel diet: an open, prospective trial. *J Am Acad Dermatol* 1993; 29: 1002–1007.
- 57 Dou X, Liu L-L, Zhu X-J. Nickel-elicited systemic contact dermatitis. *Contact Derm* 2003; 48: 126–129.
- 58 Antico A, Soana R. Chronic allergic-like dermatopathies in nickel-sensitive patients. Results of dietary restrictions and challenge with nickel salts. *Allergy Asthma Proc* 1999; 20: 235–242.
- 59 Hsu JW, Matiz C, Jacob SE. Nickel allergy: localized, id, and systemic manifestations in children. *Pediatr Dermatol* 2011; 28: 276–280.
- 60 Matiz C, Jacob SE. Systemic contact dermatitis in children: how an avoidance diet can make a difference. *Pediatr Dermatol* 2010; Epub ahead of print.
- 61 Jensen CS, Menné T, Johansen JD. Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Derm* 2006; 54: 79–86.
- 62 Wittsiepe J, Schnell K, Hilbig A, *et al.* Dietary intake of nickel and zinc by young children – results from food duplicate portion measurements in comparison to data calculated from dietary records and available data on levels in food groups. *J Trace Elem Med Biol* 2009; 23: 183–194.
- 63 De Medeiros LM, Fransway AF, Taylor JS, *et al.* Complementary and alternative remedies: an additional source of potential systemic nickel exposure. *Contact Derm* 2008; 58: 97–100.
- 64 Fowler JF Jr. Systemic contact dermatitis caused by oral chromium picolinate. *Cutis* 2000; 65: 116.
- 65 Kaaber K, Menné T, Tjell JC, *et al.* Antabuse® treatment of nickel dermatitis. Chelation – a new principle in the treatment of nickel dermatitis. *Contact Derm* 1979; 5: 221–228.

- 66 Kaaber K, Menné T, Veien N, *et al.* Treatment of nickel dermatitis with Antabuse®; a double blind study. *Contact Derm* 1983; 9: 297–299.
- 67 Fowler JF Jr. Disulfiram is effective for nickel allergic hand eczema. *Am J Contact Derm* 1992; 3: 175–178.
- 68 Sharma AD. Disulfiram and low nickel diet in the management of hand eczema. A clinical study. *Indian J Dermatol Venereol Leprol* 2006; 72: 113–118.
- 69 Van Hoogstraten IM, Boos C, Boden D, *et al.* Oral induction of tolerance to nickel sensitization in mice. *J Invest Dermatol* 1993; 101: 26–31.
- 70 Van Hoogstraten IMW, Andersen KE, Von Blomberg BME, *et al.* Reduced frequency of nickel allergy upon oral nickel contact at an early age. *Clin Exp Immunol* 1991; 85: 441–445.
- 71 Mortz CG, Lauritsen JM, Bindslev-Jensen C, *et al.* Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. *Acta Dermatol Venereol* 2002; 82: 359–364.
- 72 Panzani RC, Schiavino D, Nucera E, *et al.* Oral hyposensitization to nickel allergy: preliminary clinical results. *Int Arch Allergy Immunol* 1995; 107: 251–254.
- 73 Morris DL. Intradermal testing and sublingual desensitization for nickel. *Cutis* 1998; 61: 129–132.
- 74 Schiavino D, Nucera E, Alonzi C, *et al.* A clinical trial of oral hyposensitization in systemic allergy to nickel. *Int J Immunopathol Pharmacol* 2006; 19: 593–600.
- 75 Tammaro A, De Marcho G, Persechino S. Allergy to nickel: first results on patients administered with an oral hyposensitization therapy. *Int J Immunopathol Pharmacol* 2009; 22: 837–840.
- 76 Minelli M, Schiavino D, Musca F. Oral hyposensitization to nickel induces clinical improvement and a decrease in Th1 and Th2 cytokines in patients with systemic nickel allergy syndrome. *Int J Immunopathol Pharmacol* 2010; 23: 193–201.
- 77 Kuroishi T, Kinbara M, Sato N, *et al.* Biotin status affects nickel allergy via regulation of interleukin-1β production in mice. *J Nutr* 2009; 139: 1031–1036.
- 78 Veien NK, Hattel T, Laurberg G. Placebo-controlled oral challenge with cobalt in patients with positive patch tests to cobalt. *Contact Derm* 1995; 33: 54–55.
- 79 Asano Y, Makino T, Norisugi O, *et al.* Occupational cobalt induced systemic contact dermatitis. *Eur J Dermatol* 2009; 19: 166–194.
- 80 Stuckert J, Nedorost S. Low-cobalt diet for dyshidrotic eczema patients. *Contact Derm* 2008; 59: 361–365.
- 81 Kaaber K, Veien NK. The significance of chromate ingestion in patients allergic to chromate. *Acta Dermatol Venereol* 1977; 57: 321–323.
- 82 Veien NK, Hattel T, Laurberg G. Chromate-allergic patients challenged orally with potassium dichromate. *Contact Derm* 1994; 31: 137–139.
- 83 Sharma AD. Low chromate diet in dermatology. *Indian J Dermatol* 2009; 54: 293–295.
- 84 Oh C-K, Jo J-H, Jang H-S, *et al.* An unusual case of mercurial baboon syndrome from metallic mercury in a broken industrial barometer. *Contact Derm* 2003; 49: 309–310.
- 85 Lerch M, Bircher AJ. Systemically induced allergic exanthem from mercury. *Contact Derm* 2004; 50: 349–353.
- 86 Möller H, Ohlsson K, Linder C, *et al.* The flare-up reactions after systemic provocation in contact allergy to nickel and gold. *Contact Derm* 1999; 40: 200–204.
- 87 Möller H, Björkner B, Bruze M, *et al.* Laser Doppler perfusion imaging for the documentation of flare-up in contact allergy to gold. *Contact Derm* 1999; 41: 131–135.
- 88 Möller H. Contact allergy to gold as a model for clinical-experimental research. *Contact Derm* 2010; 62: 193–200.
- 89 Schaffran RM, Storrs FJ, Schallock P. Prevalence of gold sensitivity in asymptomatic individuals' gold dental restorations. *Am J Contact Derm* 1999; 10: 201–206.
- 90 Ekqvist S, Svedman C, Möller H, *et al.* High frequency of contact allergy to gold in patients with endovascular coronary stents. *Br J Dermatol* 2007; 157: 730–738.
- 91 Ekqvist S, Svedman C, Lundh T, *et al.* A correlation found between gold concentration in blood and patch test reactions in patients with coronary stents. *Contact Derm* 2008; 59: 137–142.
- 92 Svedman C, Ekqvist S, Möller H, *et al.* A correlation found between contact allergy to stent material and restenosis of the coronary arteries. *Contact Derm* 2009; 60: 158–164.
- 93 Kleinhans D, Knoth W. Paraben-Kontaktallergie mit enteraler Provokation. *Z Hautkr* 1973; 48: 699–701.
- 94 Sánchez-Pérez J, Díez MB, Pérez AA, *et al.* Allergic and systemic contact dermatitis to methylparaben. *Contact Derm* 2006; 54: 117–128.
- 95 Veien NK, Hattel T, Laurberg G. Oral challenge with parabens in paraben-sensitive patients. *Contact Derm* 1996; 34: 433.
- 96 Roed-Petersen J, Hjorth N. Contact dermatitis from antioxidants. *Br J Dermatol* 1976; 94: 233–241.
- 97 Dejobert Y, Delaporte E, Piette F, *et al.* Vesicular eczema and systemic contact dermatitis from sorbic acid. *Contact Derm* 2001; 45: 291.
- 98 Lowther A, McCormick T, Nedorost S. Systemic contact dermatitis from propylene glycol. *Dermatitis* 2008; 19: 105–108.
- 99 Hill AM, Belsito DV. Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame? *Contact Derm* 2003; 49: 258–272.
- 100 Hosoki M, Bando E, Asaoka K, *et al.* Assessment of allergic hypersensitivity to dental materials. *Biomed Mater Eng* 2009; 19: 53–61.
- 101 Veien NK, Borchhorst E, Hattel T, *et al.* Stomatitis or systemically induced contact dermatitis from metal wire in orthodontic materials. *Contact Derm* 1994; 30: 210–211.
- 102 Schultz JC, Connelly E, Glesne L, *et al.* Cutaneous and oral eruption from oral exposure to nickel in dental braces. *Dermatitis* 2004; 15: 154–157.

- 103 Guimaraens D, Gonzalez MA, Condé-Salazar L. Systemic contact dermatitis from dental crowns. *Contact Derm* 1994; 30: 124-125.
- 104 Chen AY, Zirwas MJ. Denture stomatitis. *Skinmed* 2007; 6: 92-94.
- 105 Thyssen JP, Jakobsen SS, Engkilde K, *et al.* The association between metal allergy, total hip arthroplasty, and revision. A case-control study. *Acta Orthopaedica* 2009; 80: 646-652.
- 106 Antony FC, Dudley W, Field R, *et al.* Metal allergy resurfaces in failed hip endoprostheses. *Contact Derm* 2003; 48: 49-50.
- 107 Hallab NJ, Anderson S, Caicedo M, *et al.* Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty. *J Arthroplasty* 2004; 19: 88-93.
- 108 Hallab NJ, Caicedo M, Epstein R, *et al.* *In vitro* reactivity to implant metals demonstrates a person-dependent association with both T-cell and B-cell activation. *J Biomed Mater Res* 2010; 92A: 667-682.
- 109 Cadosch D, Chan E, Gautschi P, *et al.* Metal is not inert: role of metal ions released by biocorrosion in aseptic loosening – current concepts. *J Biomed Mater Res* 2009; 91A: 1252-1262.
- 110 Thomas P, Schuh A, Eben R, *et al.* Allergy to bone cement components. *Orthopade* 2008; 37: 117-120.
- 111 Haddad FS, Cobb AG, Bentley G, *et al.* Hypersensitivity in aseptic loosening of total hip replacements. *J Bone Joint Surg* 1996; 78B: 546-549.
- 112 Averbeck M, Gebhardt C, Simon JC, *et al.* Resolution of both persistent eczema and implant failure following removal of nickel containing implant. *J Eur Acad Dermatol Venereol* 2009; 23: 1197-1223.
- 113 Nosbaum A, Rival-Tringali AL, Barth X, *et al.* Nickel-induced systemic allergic dermatitis from a sacral neurostimulator. *Contact Derm* 2008; 59: 319-320.
- 114 Grange-Prunier A, Frances C, Badet B, *et al.* Dermite de contact systémique au nickel induite par un cathéter veineux. *Ann Dermatol Vénéréol* 2008; 135: 743-747.
- 115 Bircher AJ, Schmidli F, Stub C, *et al.* Systemic allergic dermatitis reaction to nickel released from an eyelet in an intravenous catheter. *Contact Derm* 2009; 61: 180-182.
- 116 Gao X, He RX, Yan SG, *et al.* Dermatitis associated with chromium following total knee arthroplasty. *J Arthroplasty* 2011; 26: 13-16.
- 117 Dietrich KA, Maxooschian F, Summer B, *et al.* Intolerance reactions to knee arthroplasty in patients with nickel/cobalt allergy and disappearance of symptoms after revision surgery with titanium-based endoprostheses. *J Dtsch Dermatol Ges* 2009; 7: 410-413.
- 118 Thyssen JP, Menné T, Schalock PC, *et al.* Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. *Br J Dermatol* 2011; 164: 473-478.
- 119 Thomas P, Schuh A, Ring J, *et al.* Orthopedic surgical implants and allergies: joint statement by the implant allergy working group (AK 20) of the DGOOC (German association of orthopedics and orthopedic surgery) DKG (German contact dermatitis research group) and dgaki (German society for allergology and clinical immunology). *Orthopade* 2008; 37: 75-88.
- 120 Hindsén M, Bruze M, Christensen OB. Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions. *J Am Acad Dermatol* 2001; 44: 616-623.
- 121 Guerra L, Rogkakou A, Massacane P, *et al.* Role of contact sensitization in chronic urticaria. *J Am Acad Dermatol* 2007; 56: 88-90.
- 122 Magen E, Mishal J, Menachem S. Impact of contact sensitization in chronic spontaneous urticaria. *Am J Med Sci* 2011; 341: 202-206.
- 123 di Gioacchino M, Boscolo P, Cavallucci E, *et al.* Lymphocyte subset changes in blood and gastrointestinal mucosa after oral nickel challenge in nickel-sensitized women. *Contact Derm* 2000; 43: 206-211.
- 124 Jensen CS, Lisby S, Larsen JE, *et al.* Characterization of lymphocyte subpopulations and cytokine profiles in peripheral blood of nickel-sensitive individuals with systemic contact dermatitis after oral nickel exposure. *Contact Derm* 2004; 50: 31-38.
- 125 Summer B, Paul C, Mazooschian F, *et al.* Nickel (Ni) allergic patients with complications to Ni containing joint replacement show preferential IL-17 type reactivity to Ni. *Contact Derm* 2010; 63: 15-22.
- 126 Rau C, Thomas P, Thomsen M. Metal sensitivity in patients with joint replacement arthroplasties before and after surgery. *Orthopade* 2008; 37: 102-110.
- 127 Davies AP, Willert HG, Campbell PA, *et al.* An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. *J Bone Joint Surg Am* 2005; 87: 18-27.
- 128 Thomas P, Braathén LR, Dörig M, *et al.* Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy* 2009; 64: 1157-1165.
- 129 Park YS, Moon YW, Lim SJ, *et al.* Early osteolysis following second-generation metal-on-metal hip replacement. *J Bone Joint Surg Am* 2005; 87: 1515-1521.
- 130 Thomas P, Gollwitzer H, Maier S, *et al.* Osteosynthesis associated contact dermatitis with unusual perpetuation of hyperreactivity in a nickel allergic patient. *Contact Derm* 2006; 54: 222-225.
- 131 Thomas P, Bandl W-D, Maier S, *et al.* Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness *in vitro*: case report and review of the literature. *Contact Derm* 2006; 55: 199-202.
- 132 White JML, Goon ATJ, Jowsey IR, *et al.* Oral tolerance to contact allergens: a common occurrence? A review. *Contact Derm* 2007; 56: 247-254.
- 133 Hindson C. Contact eczema from methyl salicylate reproduced by oral aspirin/acetylsalicylic acid. *Contact Derm* 1977; 3: 348-349.

- 134 Gallo R, Parodi A. Baboon syndrome from 5-aminosalicylic acid. *Contact Derm* 2002; **46**: 110.
- 135 Hayakawa R, Ogino Y, Aris K, *et al.* Systemic contact dermatitis due to amlexanox. *Contact Derm* 1992; **27**: 122.
- 136 de Groot AC, Conemans J. Allergic urticarial rash from oral codeine. *Contact Derm* 1986; **14**: 209–214.
- 137 Alonso R, Enrique E, Cisteró A. Positive patch test to diclofenac in Stevens-Johnson syndrome. *Contact Derm* 2000; **42**: 367.
- 138 Fernandez RV, Casas L, Taboada M, *et al.* Systemic contact dermatitis from erythromycin. *Contact Derm* 1994; **30**: 311.
- 139 Ravenscroft J, Goulden V, Wikinson M. Systemic allergic contact dermatitis to 8-methoxypsoralen (8-MOP). *J Am Acad Dermatol* 2001; **45**: S218–S219.
- 140 Lechner T, Gryntzman B, Bäurle G. Hämatogenes allergische Kontaktekzem nach oraler Gabe von Nystatin. *Mycosen* 1987; **30**: 143–146.
- 141 Cooper SM, Reed J, Shaw S. Systemic reaction to nystatin. *Contact Derm* 1999; **41**: 345–346.
- 142 Panhans-Gross A, Gall HI, Peter R-U. Baboon syndrome after oral penicillin. *Contact Derm* 1999; **41**: 352–353.
- 143 Pigatto PD, Morelli M, Potenghi MM, *et al.* Phenobarbital-induced allergic dermatitis. *Contact Derm* 1987; **16**: 279.
- 144 Tomb R, Lepoittevin JP, Espinassonze F, *et al.* Systemic contact dermatitis from pseudoephedrine. *Contact Derm* 1991; **24**: 86–88.
- 145 Sánchez TS, Sánchez-Pérez J, Aragüés M, *et al.* Flare-up reaction of pseudoephedrine baboon syndrome after positive patch test. *Contact Derm* 2000; **42**: 312–313.
- 146 Barbaud A, Reichert-Penetrat S, Trechot P, *et al.* Sensitization to resorcinol in a prescription verrucide preparation: unusual systemic clinical features and prevalence. *Ann Dermatol Venereol* 2001; **128**: 615–618.
- 147 Gutgesell C, Fuchs T. Orally elicited allergic contact dermatitis to tetraethylthiuramdisulfide. *Am J Contact Derm* 2001; **12**: 235–236.
- 148 Metz J, Hundertmark U, Pevny I. Vitamin C allergy of the delayed type. *Contact Derm* 1980; **6**: 172–174.
- 149 Bajaj AK, Rastogi S, Misra A, *et al.* Occupational and systemic contact dermatitis with photosensitivity due to vitamin B6. *Contact Derm* 2001; **44**: 184.
- 150 Menné T, Weismann K. Hämatogenes Kontaktekzem nach oraler Gabe von Neomycin. *Der Hautarzt* 1984; **35**: 319–320.

Answers

- 1 (e)
- 2 (a)
- 3 (a)
- 4 (a + b)
- 5 (c)
- 6 (d)
- 7 (a + d)
- 8 (d)
- 9 (c)
- 10 (a)