ACTA DERMATO-VENEREOLOGICA
SUPPLEMENTUM 147

Systemically Induced Eczema in Adults

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Distributed by The Almqvist & Wiksell Periodical Company, Stockholm, Sweden

Denne afhandling er i forbindelse med omstående tidligere publicerede artikler af det lægevidenskabelige fakultet ved Københavns Universitet antaget til offentligt at forsvares for den medicinske doktorgrad.
København, den 29. juni 1989

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Dekan

This thesis, together with the following previously published papers, has been accepted by the Medical Faculty of the University of Copenhagen to be defended in public for the medical doctorate.
Copenhagen, June 29, 1989

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Dean

Forsvaret finder sted den 17. november 1989 kl. 14 præcis i auditoriet, Medicinsk-historisk Museum, Bredgade 62, København.

This review is based on the papers listed below. The papers will be referred to in the text by Roman numeral.

I. **Veien, NK, Svejgaard E.** Lymphocyte transformation in patients with cobalt dermatitis. Br J Derm 1978; 99: 191-196.

II. **Veien NK, Hattel T, Justesen O, Nørholm A.** Oral challenge with nickel and cobalt in patients with positive patch tests to nickel and/or cobalt. Acta Derm Venereol (Stockh) 1987; 67: 321-325.

III. **Veien NK, Morling N, Svejgaard E.** *In vitro* nickel binding to mononuclear cells in peripheral blood. Acta Derm Venereol (Stockh) 1980; 61: 64-66.

IV. **Veien NK, Svejgaard E, Menné T.** *In vitro* lymphocyte transformation to nickel: A study of nickel-sensitive patients before and after epicutaneous and oral challenge with nickel. Acta Derm Venereol (Stockh) 1979; 59: 447-451.

V. **Kaaber K, Veien NK.** The significance of chromate ingestion in patients allergic to chromate. Acta Derm Venereol (Stockh) 1977; 57: 321-323.

VI. **Veien NK, Kaaber K.** Nickel, cobalt and chromium sensitivity in patients with pompholyx (dyshidrotic eczema). Contact Dermatitis 1979; 5: 371-374.

VII. **Veien NK, Hattel, Justesen O, Nørholm A.** Oral challenge with metal salts (I). Vesicular patch-test negative hand eczema. Contact Dermatitis 1983; 9: 402-406.

VIII. **Veien NK, Hattel T, Justesen O, Nørholm A.** Dietary treatment of nickel dermatitis. Acta Derm Venereol (Stockh) 1985; 65: 138-142.

IX. **Veien NK, Andersen MR.** Nickel in Danish food. Acta Derm Venereol (Stockh) 1986; 66: 502-509.

X. **Veien NK, Hattel T, Justesen O, Nørholm A.** Oral challenge with balsam of Peru. Contact Dermatitis 1985; 12: 104-107.

XI. **Veien NK, Hattel T, Justesen O, Nørholm A.** Oral challenge with food additives. Contact Dermatitis 1987; 17: 100-103.

XII. **Veien NK, Hattel T, Justesen O, Nørholm A.** Diagnostic procedures for eczema patients. Contact Dermatitis 1987; 17: 35-40.

Preface

This thesis is based on studies carried out in the Department of Dermatology of The Finsen Institute, Copenhagen, the Department of Dermatology and the Tissue Typing Laboratory, Rigshospitalet (The University Hospital), Copenhagen, The Environmental Engineering Laboratory, University of Aalborg, and in the private dermatological practice in Aalborg currently operated by A. Nørholm, T. Hattel, G. Laurberg and myself.

I am grateful for the support provided by Holger Brodthagen, former head of the Department of Dermatology of the Finsen Institute, Professor Gustav Asboe-Hansen, former head of the Department of Dermatology, Rigshospitalet, Professor Arne Svejgaard, head of the Tissue Typing Laboratory, Rigshospitalet, and Professor Jens Aage Hansen, head of the Environmental Engineering Laboratory, University of Aalborg.

I wish also to thank my co-authors, in particular Knud Kaaber who awakened my interest in systemically induced eczemas and who was the architect of the initial oral challenge studies. Else and Arne Svejgaard introduced me to in vitro immunological test procedures and placed excellent laboratory facilities at my disposal. Many fruitful discussions concerning this work took place in the Tissue Typing Laboratory as well as in Else Svejgaard's laboratory at Rigshospitalet. I am especially grateful to my partners in our practice in Aalborg who patiently discussed various aspects of the clinical studies throughout the years during which they were carried out.

Thanks are also due the staffs of the departments in which I have worked and in particular to the nurses and secretaries in our practice for careful assistance in conducting the clinical studies. I am also very grateful to the many patients who willingly participated in these studies.

I am deeply indebted to my wife Karen who translated and typed all the papers. She has been my most valued critic, and this work could not have been completed without her participation.

Financial assistance, in particular in support of the laboratory investigations, was provided by Statens Lægevidenskabelige Forskningsråd, Aalborg Kommunes Fond for Medicinsk Forskning, Sygekassernes Helsefond, Fonden af 1870, P. Carl Petersens Fond and Aalborg Stifts Julelotteri. The publication of this thesis was supported by the Winterthur-Borgen legat.

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Background of the present study

Systemically induced contact dermatitis

The oral ingestion of certain haptens in patients with eczema and cellular immunity to the same substances may cause a flare of the patient's dermatitis. Examples of such haptens include salts of the metals nickel, chromium and mercury, and medicaments like chlorpromazine, nystatin and ampicillin (Menné, 1983b; Cronin, 1972; Pirilö, 1970; Fisher, 1966; Klaschka, 1979; Fisher, 1986; Lechner et al., 1987; Andersen KE, 1988).

Allergic contact dermatitis caused by poison ivy and/or oak (Toxicodendron species) is very common in the United States, and oral hyposensitization therapy with slowly increasing doses of the sensitizing oleoresin has been attempted. 10% of a group of patients treated in this way experienced flares of dermatitis in previously affected areas of the skin after oral ingestion of the hapten. Some very sensitive patients experienced anal pruritus (Kligman, 1958). Epidemics of systemic contact dermatitis have occurred following the ingestion of cashew nuts contaminated by pieces of the shells which contain an oleoresin closely related to that of the Toxicodendron species. (Marks et al., 1984). Similar problems may occur after the ingestion of the fruit of the Ginko tree which contains substances chemically related to those described above (Becker and Skipworth, 1975).

10 of 12 neomycin-sensitive patients suffered flares of their dermatitis after oral challenge with neomycin; two also had flares of dermatitis at neomycin patch test sites. 6 of 9 hydroxyquinoline-sensitive patients experienced flares of their dermatitis after oral challenge with that compound. (Ekelund and Möller, 1969).

Dermatitis induced by the ingestion of foodstuffs

Eczema may occur in adults after the ingestion of foodstuffs to which the patient has a) an immediate-type hypersensitivity or b) a possible immune reaction which has not been demonstrated.

Some years ago, the relationship between the intake of genuine food and hand

eczema in adults was reviewed by Sultzberger and Baer (1948) who concluded that both chronic lichenified hand eczemas and recurrent vesicular hand eczemas might be induced by foodstuffs. They considered food induced hand eczemas to be rare and felt that genuine foodstuffs as well as food additives could be the cause of such reactions.

Rowe and Rowe (1972) reviewed 50 cases of hand eczema thought to be due to the ingestion of food items. In most of their patients, skin tests were negative and the actual diagnoses were based on the use of a standard elimination diet (Rowe and Rowe, 1965).

The aims of the present study

The aims of the present study were as follows:

1) to determine
   a) if uncomplicated oral challenge procedures, used routinely, can reproduce the dermatitis of patients suspected to suffer from systemically induced contact dermatitis to common contact allergens such as nickel, cobalt, chromium and the balsams, as well as dermatitis suspected to be caused by commonly used food additives,
   and
2) to determine
   a) the nickel content of commonly consumed Danish foodstuffs to enable the formulation of practical diet instructions for the treatment of certain nickel allergic patients;
   b) the distribution of various types of eczema in a general dermatological practice, and, in particular,
   c) how commonly the diagnosis of systemically induced dermatitis is made in a general dermatological practice where oral challenge procedures are used routinely.

Nickel and/or cobalt as the cause of systemic contact dermatitis in patch test positive patients

Clinical observations

Bonnevie (1939), Calnan (1956), and Marcussen (1957) described secondary eruptions in nickel allergic patients which were commonly seen at the elbow flexures, on the sides of the neck and in the anogenital region. These authors discussed the possibility of a hematogenous spread, since there was no obvious external nickel contact at these secondary sites.

There have been sporadic case reports dealing with similar eruptions attributed to microgram doses of nickel released into the circulation from infusion cannulas (Olerud, et al., 1984; Stoddart, 1960; Smeenk and Teunissen, 1977).

Experimental oral challenge

Christensen (1981) described an out-patient population of 149 consecutive nickel sensitive patients, half of whom had secondary eruptions, and found that 51 of the 66 who had hand eczema (77%) had the recurrent vesicular type of hand eczema.

In a double-blind oral challenge experiment, 9 of 12 patients experienced an aggravation of their recurrent vesicular hand eczema after challenge with 5.6 mg nickel given as nickel sulphate but not after a placebo (Christensen and Möller, 1975). A single-blind challenge with 2.8 mg and - if this did not result in a reaction - 5.6 mg nickel resulted in flares of dermatitis in 34 of 43 nickel-sensitive females (Pecegueiro and Brandao, 1982).

Similar oral challenge studies have been performed in several centers, and in most studies, challenge doses of less than 1 mg nickel have resulted in flares of dermatitis in only a few patients, while doses of 2 - 2.5 mg have resulted in flares

of dermatitis in approximately 50% of the patients (Bedello et al., 1985; Cronin et al., 1981; Jordan and King 1979; Kaaber et al., 1979; Kaaber et al., 1978; Roduner et al., 1987; Sertoli et al., 1985).

Burrows et al. (1981) found no difference between reactions to nickel and a placebo even when a dose of 4 mg nickel was given daily for 2 days, and Gawkrodger et al. (1986) found specific reactivity only when the challenge dose was as high as 5.6 mg nickel.

There has been some doubt as to the clinical significance of the flares seen after oral challenge because the dose of nickel used in most challenge experiments is higher than the amount ingested in a normal daily diet.

Twelve nickel allergic females with vesicular hand eczema were asked to follow a diet which was naturally rich in nickel (490 µg nickel per day) for 4 days. 11 days after the initiation of this diet a dermatologist who did not know at the time of the evaluation whether the patient had ingested a nickel-rich diet evaluated the severity of the dermatitis. Aggravation of the dermatitis was seen in 10 of the 12 patients (Nielsen, in press).

Absorption of orally ingested nickel sulphate has been documented by the determination of the urinary excretion of nickel over a period of several days following oral challenge with nickel sulphate (Menné, 1983b; Christensen OB, 1981; Kaaber et al., 1978; Spruit and Bongaarts, 1977).

The relationship between nickel and cobalt sensitization

The interplay between nickel and cobalt sensitivity is not clear. Simultaneous nickel and cobalt sensitization is common, particularly among nickel allergic patients with hand eczema (Menné, 1983a). Sensitization to each of the metals seems to be a specific event. By the use of a lymphocyte transformation test with T-lymphocyte enriched cell populations, it was shown that cobalt allergic patients did not react to stimulation with nickel or chromate but did react to cobalt (Al-Tawil et al., 1984). Previous attempts to demonstrate specific lymphocyte transformation in cobalt allergic patients have been successful only in strongly sensitized persons, and at that time the method could therefore not be utilized to demonstrate possible cross sensitization between nickel and cobalt (I).

Patients sensitized to both nickel and cobalt often have severe hand eczema, and animal experiments support the theory that there is a potentiating effect of simultaneous sensitization to the two substances (Rystedt and Fisher, 1983; van Joost and van Everdingen, 1981; Lammintausta et al., 1985). Oral challenge with nickel as well as cobalt in a large group of patients with positive patch tests to nickel and/or cobalt showed that among 131 patients with positive patch tests to nickel, 55 reacted to oral challenge with nickel, as compared with 23 who reacted

to the placebo or to the placebo in combination with salts of one or both metals ($\chi^2 = 18.693$, $p < 2 \times 10^{-5}$) (II). 28 of 47 patients with positive patch tests to cobalt had a flare of dermatitis after oral challenge with cobalt, compared with 5 who reacted to the placebo or to the placebo in combination with salts of one or both metals ($\chi^2 = 24.702$, $p < 10^{6}$).

Cobalt is much more readily absorbed from the gastrointestinal tract than nickel (Tietz, 1986). In the above-mentioned study (II), flares seen after oral challenge with 1 mg cobalt in 7 of 13 patients (54%) who had positive patch tests to cobalt but not to nickel served to indicate 1) that systemically induced cobalt dermatitis is a clinical entity and 2) that a single dose of 1 mg cobalt given as a salt of the metal is a useful way of carrying out an oral challenge.

Reactions to oral challenge with cobalt were seen more frequently than predicted by patch test reactivity. 4 of 34 patients (12%) with positive patch tests to nickel as well as cobalt reacted to challenge with nickel, while 10 of the 34 (29%) reacted to cobalt (Table I).

Table I. The reactivity of 144 patients to oral challenge with nickel and cobalt.

Positive Patch tests to:	Results following oral challenge					
	Ni (Ni + placebo)	Ni + Co (Ni + Co + placebo)	Co (Co + placebo)	Placebo only	Neg.	Total
Ni	31 (3)	8 (3)	8 (5)	8	31	86 (11)
Ni + Co	4 (0)	5 (1)	10 (3)	0	11	30 (4)
Co	1 (0)	1 (0)	7 (1)	0	3	12 (1)
Total	36 (3)	14 (4)	25 (9)	8	45	128 (16)

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The dose of nickel used for oral challenge

The dose of 2.5 mg nickel used for oral challenge in this study (II) was purposely higher than the expected maximum daily intake for the following reasons:

1) to overcome variations in disease activity caused by endogenous factors other than foods and by external aggravating factors. The latter were, as far as possible, kept to a minimum while the challenge experiments were carried out;

2) to overcome unknown variations in the bioavailability of nickel. The experimental addition of 5 mg nickel in the form of nickel sulphate to a Guatemalan meal and a North American breakfast inhibited nickel absorption as did the addition of nickel to various drinks. (Solomons et al., 1982). Nickel in water ingested after fasting is absorbed more completely than nickel in water ingested during a meal (Sunderman et al, 1987).
3) to overcome individual variations due to varying degrees of sensitivity to nickel;
4) because the concentration of nickel in the target organ, i.e., the skin, is largely unknown and may vary greatly due to factors other than ingested nickel, for example, sweating; there could also be intermittently high nickel concentrations in the target organ due to mobilization of nickel from the tissues or the transport of nickel to the skin by means of mononuclear cells which may bind amounts of nickel sufficient to induce lymphocyte transformation (III; Silvennoinen-Kassinen et al., 1987);
5) because intermittently high intakes of nickel may be more relevant than the mean intake, as suggested by the eruptive nature of most types of dermatitis described in the challenge study.

The oral challenge was carried out during periods when the patient's dermatitis was in a relatively stable state, and the substances were ingested with a slice of bread between meals.

The mechanism of oral challenge reactions

The reactivation of previously positive patch test sites after oral challenge indicates an antigen specific reaction and also that cellular immunity is of significance in systemic contact dermatitis (Christensen OB et al., 1981). Histological and immune histochemical examinations also suggest cellular immune reactions rather than antibody-medicated reactions (Christensen OB et al., 1985). Similarly, Möller (1984) considered flare-up reactions in sensitized mice which appeared at one site after the epicutaneous application of the hapten at another site to be due to cellular immunity.

The increased rate of lymphocyte transformation seen 2 weeks after the oral challenge of nickel sensitive patients with 4 mg nickel supports these clinical and histological findings (IV).

Christensen (1981) observed widespread flares of rapid onset in some nickel allergic patients after oral challenge. Antibodies against a nickel-albumin complex which had induced antibody formation in rabbits were found in 3 of 5 patients who had such rapid-onset flares after oral challenge (Veien et al., 1979). The

method used was rather crude and more specific investigations are needed to substantiate these results.

The complexity of reactions to oral challenge with nickel is discussed further on page 22.

Systemic contact dermatitis in patients with positive patch tests to chromium

Clinical evidence of systemic dermatitis caused by chromium

Chromium-sensitive patients often develop vesicular hand eczema, and it has been assumed that the ingestion of chromium salts can contribute to the chronicity of this type of hand eczema.

Mali (1960) demonstrated a positive Prausnitz-Küstner reaction in a chromate-sensitive patient whose vesicular hand dermatitis flared after inhalation of paint fumes containing chromate. Circumstantial evidence indicated that chromium in a dental plate caused generalized dermatitis in a chromate-sensitive patient (Hubler and Hubler 1983). Kaaber et al. (1983) described psoriasiform lesions on the elbows of chromate-sensitive patients which flared after oral challenge with 2.5 mg chromium.

Experimental oral challenge

Fregert (1965) challenged 5 chromate-sensitive patients with 50 µg potassium dichromate given orally, and all the patients experienced vesiculation of the hands within 2 hours; one also had more widespread eruptions. Schleiff (1968) challenged 20 chromate-sensitive patients with 1 to 10 mg potassium dichromate and saw flares of dermatitis and of previously positive patch test sites. A weakly chromate-sensitive patient who had vesicular hand eczema was challenged orally with 2.5 mg chromium and later 5 mg chromium. After the latter challenge a severe flare of the dermatitis was seen (Goitre et al., 1982).

In a placebo-controlled study of 31 chromate-sensitive patients, 11 experienced flares of dermatitis after ingestion of 2.5 mg chromium given as potassium dichromate. 9 of 14 patients who had recurrent vesicular hand eczema experienced flares, compared with 2 of 11 who had other types of dermatitis (V).

Sertoli et al. (1985) carried out a challenge with 50 µg potassium dichromate in a placebo-controlled study and saw a reaction in one of 3 patients. Open challenge with 2.5 mg chromium given as potassium dichromate in a routine investigation in patch test positive patients with dermatitis suspected to be systemic gave rise to flares of dermatitis in 6 of 15 patients (Veien et al., 1983).

The reactions seen following oral challenge with 50 µg potassium dichromate need to be confirmed in larger groups of patients. Until then it is suggested that 2.5 mg chromium given as potassium dichromate should be used for oral challenge.

The intake of chromium in foods has been estimated to be 25 to 300 µg per day (Anderson and Kozlovsky, 1985), and the clinical relevance of the results of the oral challenge studies remains to be determined by, for example, dietary depletion trials. One concern about such trials is that chromium is an essential element in man and that the food intake of some persons may already contain less than the recommended level (Prasad and Oberleas, 1976).

Diagnostic oral challenge with nickel, cobalt and chromium in patients with negative patch tests

The reliability of cutaneous testing with nickel

Patch testing with 5% nickel sulphate in petrolatum is generally considered a reliable test for the detection of cellular immunity to nickel (Menné, 1983a). Kieffer (1979) found a dissociation between the history of intolerance to metallic objects and patch tests with 5% nickel among a limited number of patients. Marcussen (1959) found false negative patch tests in 3% of 622 verified cases of nickel allergy and suggested the use of intradermal tests with nickel sulphate 1:10,000 when patch testing proved unexpectedly negative (Marcussen, 1963). Meneghini and Angelini (1979) found that 6.6% of 105 patients with a history of nickel allergy and negative patch tests to nickel had positive intradermal tests. In another study, most patients with a history of metal sensitivity and negative patch tests were atopics (Möller and Svensson, 1986).

Oral challenge experiments

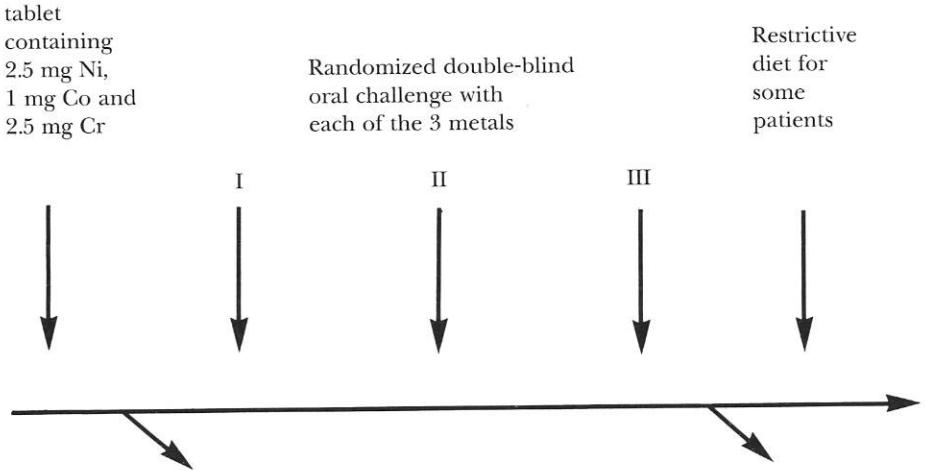
Recurrent vesicular hand eczema, which is common in patients with positive patch tests to nickel, cobalt and/or chromate, is also commonly seen in patients with negative patch tests, and a preliminary study showed that the dermatitis of some of such patients flared after oral challenge with salts of the metals, nickel, cobalt and chromium (Veien and Kaaber, 1976).

In a controlled investigation carried out to determine whether such reactivity was more than pure chance and to compare the results of oral challenge with other diagnostic tests, no correlation was found between the reactions to the oral challenge procedure, on the one hand, and the results of patch testing after stripping of the skin or intradermal testing, on the other hand (VI). The results of the

oral challenge were considered to be the most relevant diagnostic procedure because a test was considered positive when the patient's actual clinical problem was reproduced.

The test procedure depicted in Figure 1 was then used in similar large scale studies.

Figure 1:



Sequence of oral challenge procedures for patch test negative patients challenged with nickel, cobalt and chromium. If oral challenge with the mixture of metal salts did not result in a flare of dermatitis, no further challenges were carried out (left arrow angling down). If challenge with the mixture of salts was positive and challenges with none or all of the individual salts were positive, the patient was considered a placebo-reactor and no diet trial was carried out (right arrow angling down).

For the patients who experienced flares after the mixture of metal salts as well as after one or two of the individual salts, the reaction was considered specific, and if warranted by disease activity, and if the patient was willing to participate, a diet trial was instituted.

Approximately 25% of a group of 202 patients with patch test negative, recurrent vesicular hand eczema experienced flares after ingestion of the mixture as well as after one or two of the individual salts (VII). The details of the reactivity seen are given in Table II.

Table II. Reactivity to the individual metal salts among 58 of 202 patients with vesicular hand eczema and negative patch tests who reacted to 1 or 2 of the individual salts; when the same patient reacted to 2 metal salts, the numbers are connected by a dotted line.

	Ni	Co	Cr	Number of patients
Males	2	2	9	
	1	----------	1	15
		1	---------- 1	
Total number of reactions	3	3	11	
Females	15	12	6	
	3	3		43
		2	---------- 2	
	2	----------	2	
	3 (tested only with Ni)			
Total number of reactions	23	17	10	
Total number of reactions among males and females	26	20	21	Total number of patients 58

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The test method was also applied to a group of 299 patients with various long-standing dermatoses of obscure origin for whom a systemic cause of the dermatitis was suspected (Veien et al., 1983). None of 98 patients with morphologies of eczema other than hyperkeratotic hand and/or foot eczema or perianal eczema experienced any reaction. The flares seen in patients with hyperkeratotic eczema were characterized by the development of pruritic fissures, but no vesicles.

The mechanism of reaction

The mechanism of the flare of dermatitis after oral challenge of patch test negative patients is uncertain. The following possibilities should be considered: 1) a cellular immune reaction associated with a false-negative patch test; 2) a specific immunological reaction other than a cellular immune response; 3) an active immunological process which suppresses patch test reactivity but does not suppress the reaction when the hapten is presented via the gastrointestinal tract; 4) a non-immunological but specific reaction; and 5) a non-specific irritant reaction. The predominance of reactions to nickel among female patients and to chromate among male patients (Table II), a pattern which closely follows patch test reactivity, is suggestive of a specific immunological reaction and false-negative patch tests. Similarly, the flares at nickel contact sites or nickel patch test sites seen in 4 patients after the oral challenge suggest specific immunological reactivity. Since these results were published we have seen eruptions under the leather straps of a sandal in a patch test negative female patient who had a flare of vesicular hand eczema after oral challenge with chromate.

Evidence of immunological reactions other than cellular immunity, for example immune complex reactions, is best documented by the results of animal experiments like those of Polak et al. (1973) and sporadic experience in humans (Menné, 1983a). Rhinitis, asthma and vasculitis have been described as clinical features in patients with positive patch tests to nickel. Immediate-type reactions may occur in patients with no detectable cellular immune response to nickel (Mitchell, 1981; Niordson, 1981; Block and Yeung, 1982).

Unphysiologically high concentrations of nickel in serum and urine have been seen after oral challenge doses of nickel in the same range as those used in the current study. The subsequent accumulation of nickel in sweat could lead to irritant concentrations of nickel in palmar skin. Since 10% or less of ingested nickel is absorbed, unabsorbed nickel could give rise to irritant reactions on perianal skin.

The role of dietary nickel in nickel sensitive patients

Nickel homeostasis

The absorption of nickel from the gastrointestinal tract accounts for 1-10% of the amount ingested (Natl Acad Sci, 1975). Knowledge of the bioavailability of ingested nickel salts is sparse. It is known that phytic acid complexes are found in oats and that other chelate bindings are seen in some vegetables (Vohra et al., 1965). Nickel ingested after fasting is more completely absorbed than nickel ingested at a meal (Solomons et al., 1982; Sunderman et al., 1987). The absorption rate, or the mobilization of nickel from the tissues, can be altered by the ingestion of drugs like indomethacin, which increased the urinary excretion of nickel of a nonhypersensitive person from 1 to 9 µg/l urine (Spruit, 1979) or Antabuse® (disulfiram) which splits into 2 molecules of diethyldithiocarbamate in the intestine. The latter compound binds nickel in a chelate fashion and is the treatment of choice for nickel poisoning (Sunderman, 1977). Disulfiram can be an effective treatment for nickel dermatitis. (Kaaber et al., 1983; Christensen OB and Kristensen, 1982; Christensen JD, 1982; Menné and Kaaber, 1978; Spruit et al., 1978).

Complex binding of nickel to tetracyclines has also been described (Baker and Brown, 1966). There is an interrelationship between nickel and zinc as suggested by animal experiments, but it is not clear whether competitive inhibition in fact takes place and whether this has clinical significance (Spears et al., 1978; Ling and Leach, 1979).

The role of internal nickel. Clinical observations

In addition to the flares of dermatitis seen after experimental oral challenge with nickel, the evidence for the role of systemically administered nickel in causing flares of dermatitis also includes the reactions seen following the initial dose of Antabuse® given for the treatment of nickel allergy. In one study, 9 of 11 patients

experienced flares of dermatitis 1 to 7 days after the initiation of Antabuse® treatment. These flares were commonly more severe than the flares seen after oral challenge with 2.5 mg nickel. An associated increase in serum nickel and in the urinary excretion of nickel were also seen (Kaaber et al., 1979). This type of reaction is probably due to the release of nickel from a nickel-albumin or a nickel histidine complex in serum (Andersen KE et al., 1987).

Disulfiram has been seen to cause flares of dermatitis in cobalt and nickel sensitive patients when the drug was used as an adjuvant for the treatment of chronic alcoholism (Grøndahl-Hansen and Menné, 1987; Menné, 1985; Veien, 1987).

In a study of 4 nickel sensitive females Menné and Thorboe (1976) found increased urinary excretion of nickel during flares of vesicular hand eczema as compared with more quiescent periods.

The evidence against the role of ingested nickel is based largely upon a lack of reactivity in the skin after oral challenge with doses of nickel in the range of the average daily intake of nickel and on a detailed study of a very hypersensitive female whose serum and urine concentrations of nickel could not be well correlated to the activity of the dermatitis (De Jongh et al., 1978; De Jongh and Spruit, 1978).

Dietary depletion studies

In an open study, a restrictive diet was prescribed for a group of 17 patients whose dermatitis had flared after ingestion of 2.5 mg nickel (Kaaber et al., 1978). The dermatitis of 9 patients improved after the diet was followed for 6 weeks. During the diet trial, there was a decrease in the urinary excretion of nickel both among those patients who experienced improvement and among those who did not.

The eczema of one nickel sensitive patient cleared after she had followed a low-nickel diet for 6 months, and the levels of nickel in her blood and urine decreased to less than half the pre-diet values during the diet period (Gawkrodger et al., 1988).

An open diet trial was carried out among a larger group of patients with various morphologies of dermatitis consistent with systemic contact dermatitis, as well as both patch test positive and patch test negative patients. The latter were included if their dermatitis had been aggravated following oral challenge with nickel (VIII). Table III shows the types of dermatitis among the patch test positive patients.

Table III. Clinical types of dermatitis among 675 consecutive patients with positive patch tests to nickel.
In parentheses the number of patients placed on a nickel restrictive diet. 4 men and 40 women had eczema at more than 1 site, the sum of locations is, therefore, higher than the number of patients.

	Men n = 49 (11)	Women n = 626 (148)	Total n = 675 (159)
Hand and/or foot eczema	27 (7)	280 (97)	307 (104)
Ano-genitial eczema	4 (2)	20 (9)	24 (11)
Vasculitis	2 (1)	12 (11)	14 (12)
Eczema of eyelids	1 (1)	11 (5)	12 (6)
Axillary eczema	1 (1)	15 (6)	16 (7)
Other types of eczema (usually at sites of nickel contact	18 (1)	331 (32)	349 (33)

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88 (59%) of 150 patients who responded to a questionnaire follow-up carried out 1 to 5 years after the trial experienced long-term improvement after diet treatment (95% confidence limits 50-67%).

The dermatitis of only 32 of the patients cleared completely. The remainder continued to have episodic flares of dermatitis, but these were less frequent, less intense and of shorter duration than before diet treatment.

90 of the 150 patients had continued to follow the diet constantly or intermittently for 1 to 5 years. This indicates that diet treatment is suppressive rather than curative and that long-term or intermittent diet treatment is necessary. Some of the patients could regulate the severity of their dermatitis by means of a more or less restrictive diet. If persistent recurrences were seen, it was typically necessary to resume a rather restrictive diet for 1 to 2 months to control the dermatitis.

Diet trials of the type described here present problems of interpretation because of the uncontrolled nature of the study. Properly controlled studies lasting as long as it takes to determine the efficacy of this type of diet treatment are, however, extremely difficult to carry out. It was therefore decided to rely on a long-term questionnaire follow-up to substantiate the results.

Nickel in foodstuffs

Nickel in the environment

Nickel enters the human body mainly via food items, including drinking water, but also via inhalation and cutaneous contact.

The inhalation of nickel is generally limited. However, since 30 to 50% of the nickel inhaled is absorbed by the body, the pulmonary route of introduction into the organism may be of significance in special situations (Sunderman et al., 1986).

The application of ^{57}nickel on human skin showed cutaneous absorption to be more than 50% (Norseth and Piscator, 1979).

There is little accumulation of nickel in animal tissue, and the ingestion of plant foods therefore plays the greatest role in supplying the human body with nickel. Some plants are able to concentrate nickel (Brooks, 1980), but, generally speaking, the nickel content of vegetable food items reflects the nickel content of the soil in a particular area.

Experimental watering of cabbage with water to which nickel was added resulted in an increase in the nickel content of the plants (Christensen OB, 1979).

It is likely that the nickel load of the soil used for vegetable farming is increasing with increased urbanization. In Denmark, the amount of nickel in the atmosphere is estimated to be 7 g per hectare in rural areas, 15 g per hectare in the periphery of Copenhagen and 38 g per hectare in the center of Copenhagen (Akad Tekn Videnskab, 1984).

With levels below 20 µg/l, water taken from a tap after flushing generally contributes very little to nickel intake (Gammelgaard and Andersen, 1985; Nebenführer et al., 1984). Water which stands in the tap pipes can be contaminated with levels up to 490 µg in the first 250 ml of water (Andersen KE et al., 1983).

Nickel was found by spot test in a number of kitchen utensils sold in Denmark (Statens Husholdningsråd, 1984). It can be released from stainless steel and other cooking utensils at acid pH in amounts of 20-40 µg (Brun, 1979; Iliano and De Plaen, 1982, Christensen and Möller, 1978; Flyvholm et al., 1984).

The basis for the diet instructions

An analysis of the nickel content of foodstuffs available in Denmark was made with an emphasis on foods presumed to contribute significantly to nickel intake (IX).

More than 1 mg nickel per kg fresh weight was found in tea leaves, cocoa, soy meal, sunflower seeds, oatmeal, hazel nuts, beans and other seeds used for sprouts, peanuts, licorice and some sandwich spreads. There appeared to be no significant introduction of nickel into industrially processed and tinned foods. The diet instructions given in the appendix were prepared on the basis of these results and other recent studies of the nickel content of foods, as well as on the foods listed as aggravating factors in the questionnaires returned by those who had followed a low nickel diet. (Myron et al., 1978; Ellen et al., 1978; Kirkpatrick and Coffin, 1975; Koivistoinen, 1980; Andersen and Hansen, 1984; VIII).

The 24-hour intake of nickel

The food consumed during 3 24-hour periods by 8 volunteers was analyzed for nickel content. When a normal diet was followed, the mean intake of nickel was 0.13 mg/24 hrs.; the mean intake when the low nickel diet presented in the appendix was followed was 0.07 mg/24 hrs., and when a diet rich in nickel was followed, the mean was 0.25 mg/24 hrs. There was a statistically significant difference between the mean for the low nickel diet and a normal diet ($p<0.01$, Wilcoxon's test for pair differences) and between the mean for the diet rich in nickel and a normal diet ($p<0.05$, Wilcoxon's test for pair differences).

The amounts of nickel found in the 24-hour portions of food are in agreement with the amounts calculated by Flyvholm et al. (1984) in Denmark and are comparable to the experimental diet intakes determined by Myron et al. (1978) in the U.S. These values are lower than those previously published, (Schroeder et al., 1961) and may reflect more accurate methods of analysis as well as individual variations in patterns of food consumption.

The significance of the ingestion of balsams in patients with eczema

Balsam of Peru

Balsam of Peru is the concentrated sap obtained after scarification of the bark of a tree (Myroxylon perlirae), and its composition varies. Standardization is based upon the physical characteristics of the compound and identification of a few of the major chemical compounds it contains (Pharmacopoea Nordica, 1963; Wallis, 1976; Ramstad, 1959). In spite of its poorly defined chemical composition, the compound has proven useful as a screening agent in battery patch testing. It can, however, be necessary to test with a range of other substances to document sensitivity to fragrances or flavorings of the types present in balsam of Peru (Rudzki and Grzywa, 1977; Mitchell et al., 1976).

Clinical evidence for systemic reactions to balsams

Hjorth (1961) pointed out that a number of the 30 to 40 chemical compounds present in balsam of Peru are identical or closely related to chemicals present in foods, in particular in flavorings. Two balsam sensitive girls had flares of dermatitis after eating sweets (Hjorth, 1961) and one other patient experienced a flare of chronic hand eczema after consumption of a jar of orange marmelade (Hjorth, 1971).

Oral challenge studies

Oral challenges carried out with 20-50 mg of balsam of Peru have resulted in flares of dermatitis in only a few patients. Challenges with individual spices have given rise to occasional flares of dermatitis and/or urticaria (Fisher, 1975; Forsbeck and Skog, 1977; Niinimöki and Hannuksela, 1981; Bedello et al., 1982; Warin and Smith, 1982).

42 patients with eczema suspected to have an endogenous cause and for whom patch testing had not disclosed the cause were challenged orally in an open study with 900 mg of balsam of Peru in capsules. 9 experienced flares of their dermatitis. (Veien et al., 1983).

A double-blind, placebo-controlled oral challenge procedure was carried out with a relatively high dose of 1 g of balsam of Peru (X). This dose was chosen since there could be reactivity to one of the components of balsam of Peru occurring in a relatively low concentration. A dose of this size is considered to be safe for consumption (List and Hörhammer, 1976).

In spite of a statistically significant reactivity to the challenge procedure in patients with various types of eczema (Table IV), the overall low reactivity among those who did not have positive patch tests to balsam of Peru limits the practical value of the oral challenge with balsam of Peru as a screening procedure.

Table IV. Results of oral challenge with balsam of Peru among 210 patients who completed the challenge procedure.

Positive reaction to challenge with:	Patch test positive patients			Patch test negative patients					
	balsam of Peru n = 17 (4)	wood tar, perfume mixture and/or colophony n = 26 (9)	other substances n = 13 (2)	vesicular hand eczema n = 58	anogenital eczema n = 18	axillary eczema n = 8	other types of hand eczema n = 34	various n = 36	total n = 211
balsam of Peru	10 (4)	6 (3)	1 (0)	12	5	3	3	3	45
placebo	1 (0)	1 (0)	1 (0)	3	2	0	3	4	15
balsam of Peru as well as placebo	0 (0)	2 (0)	0 (0)	1	0	0	1	1	5

The number of patch-test-positive patients with vesicular hand eczema is given in parentheses.
There was a statistically significant difference between the reactions to balsam of Peru and placebo for all patients with positive patch tests to balsam of Peru ($p<0.05$), for patients with patch-test negative vesicular hand eczema ($p<0.05$), and for the total number of patients ($p<0.01$) (sign test).

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The mechanism of the challenge reaction remains unknown. It may be immunologically based or is perhaps caused by direct action on mediators of inflammation. The latter type of reactivity has previously been suggested in patients with urticaria and reactions to oral challenge with benzoates (Juhlin, 1980). Various benzoates are present in balsam of Peru.

The relatively high dose of balsam of Peru could be expected to cause non-specific reactions similar to the immediate-type reactions seen after patch testing (Forsbeck and Skog, 1977).

Until challenge experiments have been carried out with the individual components of balsam of Peru, the challenge procedure described here should be considered rather crude. A single-dose challenge with a complex compound in which the individual components are present in unknown quantities leaves much to be desired as a diagnostic test.

A balsam restricted diet

The results of a questionnaire follow-up indicated that 47% (95% confidence limits 34-60%) of the patients placed on a balsam restrictive diet showed long-term improvement (Veien et al., 1985).

The diet instructions used were based mainly on information provided by Hjorth (1961) and Fregert (1981) and a computerized retrieval system developed by Malten. (Print-outs were kindly supplied by Professor Klaus Malten).

There is limited knowledge of the presence of balsams in food, and in order to restrict their intake effectively it may be necessary to restrict the intake of a far more varied range of foods. Terpenes, for example, are chemically related to balsams and are found in a much wider range of food items than those listed in the current study (Wilkinson, 1970).

Food additives as the cause of or an aggravating factor in eczema

Clinical observations

Food induced eczema of the hands of adults has been linked to atopic dermatitis (Sultzberger and Baer, 1948; Rowe and Rowe, 1972). The causative food items include classical food allergens such as eggs, milk, wheat, beef, pork, and commonly also foods which are known to contain or release biogenic amines or other vasoactive substances. It has been suggested that the adverse effects of many food additives are due to direct action on mediators of inflammation, and there is some experimental evidence to support this assumption (Benton and Barnetson, 1985; Nain, 1983). Increased plasma histamine levels were seen among a group of children who reacted to oral challenge with various food items (Sampson and Jolie, 1984).

Vasoactive substances are found in foods such as citrus fruit, apples, strawberries, legumes, tomatoes, nuts, coffee, tea, beer wine, shellfish, mackerel, tuna fish, herring, aged cheese and food coloring and preservatives (Horwitz et al., 1964; Granerus et al., 1969; Rajka, 1975; Lessof et al., 1980; Alme, 1981; Buckley and Metcalfe, 1982; Kajosaari, 1982; Minford et al., 1982; Amer Acad of Allergy and Immunol, 1984; Graham et al., 1984).

Some patients with chronic eczemas which, morphologically, could be of endogenous origin benefit from restriction of the intake of classical food allergens as well as foods which contain or release biogenic amines (Veien et al., 1987a). Artificially colored and preserved foods, including soft drinks, candy and salami, were commonly listed by the patients as causing flares of their dermatitis.

Particular problems seen among coffee drinkers are detailed in a recent communication (Veien et al. 1987b).

Oral challenge with food additives

In 101 eczema patients for whom food additives were suspected to aggravate the dermatitis, oral challenge was carried out in a double-blind, placebo-controlled trial with commonly used food additives (XI). There was no statistically significant difference between 98 (of 404) reactions to active substances compared with 16 (of 101) reactions to the placebo. ($\chi^2 = 3.274$, $p = 0.07$).

Previously conducted challenge experiments with similar substances in non-selected patients with atopic dermatitis or contact dermatitis did not contribute very much to the diagnostic work up (Østergaard, 1986; Hannuksela and Lahti, 1986). A placebo-controlled challenge procedure with food additives as well as genuine foods did, however, prove useful in children with migraine headaches (Egger et al., 1983). In a study by Michaëlsson et al. (1974) the purpura of 7 patients was aggravated following placebo-controlled oral challenge with azo-dyes and benzoates.

The eczema of 12 of 20 patients with positive patch tests to p-phenylene diamine, compared with 2 of 20 controls, flared after oral challenge with 15 to 210 mg azo-dyes (Baer and Leider, 1949). Meneghini and Angelini (1978) challenged 18 p-amino-sensitive patients orally with 20 mg tartrazine and saw no reactivity.

It is possible that the doses of food additives selected for the current study (XI) were insufficient. Estimates of the daily intake of food additives vary greatly. Tartrazine intake has been estimated at 10 mg daily in the U.S. and Great Britain (Drug and Therapeutics Bull., 1980; Statens Levnedsmiddelinst, 1980). Peak intake, however, could be considerably higher and might be more significant to the precipitation of flares of dermatitis.

Other food additives, like sulfites and nitrites which were not used in this study, could be of importance. (Freedman, 1980; Henderson and Raskin, 1972; Moneret-Vautrin et al., 1980; Div of Food and Color Additives, 1985; Simon, 1986).

The distribution of various types of eczema in a general dermatological practice

Distribution of the diagnosis of eczema

Most textbook information concerning the distribution of various types of eczema is based on the patients seen in departments of dermatology (Rook et al., 1979).

Christophersen (1984) surveyed a single-day sample of the patients seen in nearly all the dermatological practices in Denmark. Seborrhoeic dermatitis accounted for 29% of the 817 eczema patients, while 21% of the patients had contact dermatitis, and 10% had atopic dermatitis. 34% of the patients had other types of eczema.

A prospective study of the diagnoses of 7887 consecutive patients with eczema in a private dermatological practice showed that the most common types of eczema were seborrhoeic dermatitis (17%), contact dermatitis (16.7%), atopic dermatitis (13%) and nummular eczema (10%). 2549 patients (32%) were given a diagnosis of non-specific eczema (XII).

Most diagnoses of eczema were made without the use of investigative procedures. This applied in particular to patients with seborrhoeic dermatitis and atopic dermatitis, while most patients with a final diagnosis of contact dermatitis were patch tested.

The results of diagnostic tests

Diagnostic tests carried out among the 7887 eczema patients showed that 897 of 3164 patients patch tested with the Standard Series of the International Contact Dermatitis Research Group had one or more positive tests, and the results of these tests were considered to be of current relevance for 545 patients. A number of positive patch test results were listed as being of unknown relevance, and more patients might have received a final diagnosis of allergic contact dermatitis had

we known more about the presence in the environment of the substances in question. The distribution of contact allergens was similar to that described previously (Magnusson et al., 1968; Hammershøy, 1980; Veien et al., 1982) except that few positive patch tests to chromate were recorded among male patients. A similar paucity of allergic contact dermatitis to chromate was recently noted by van Ketel (1984).

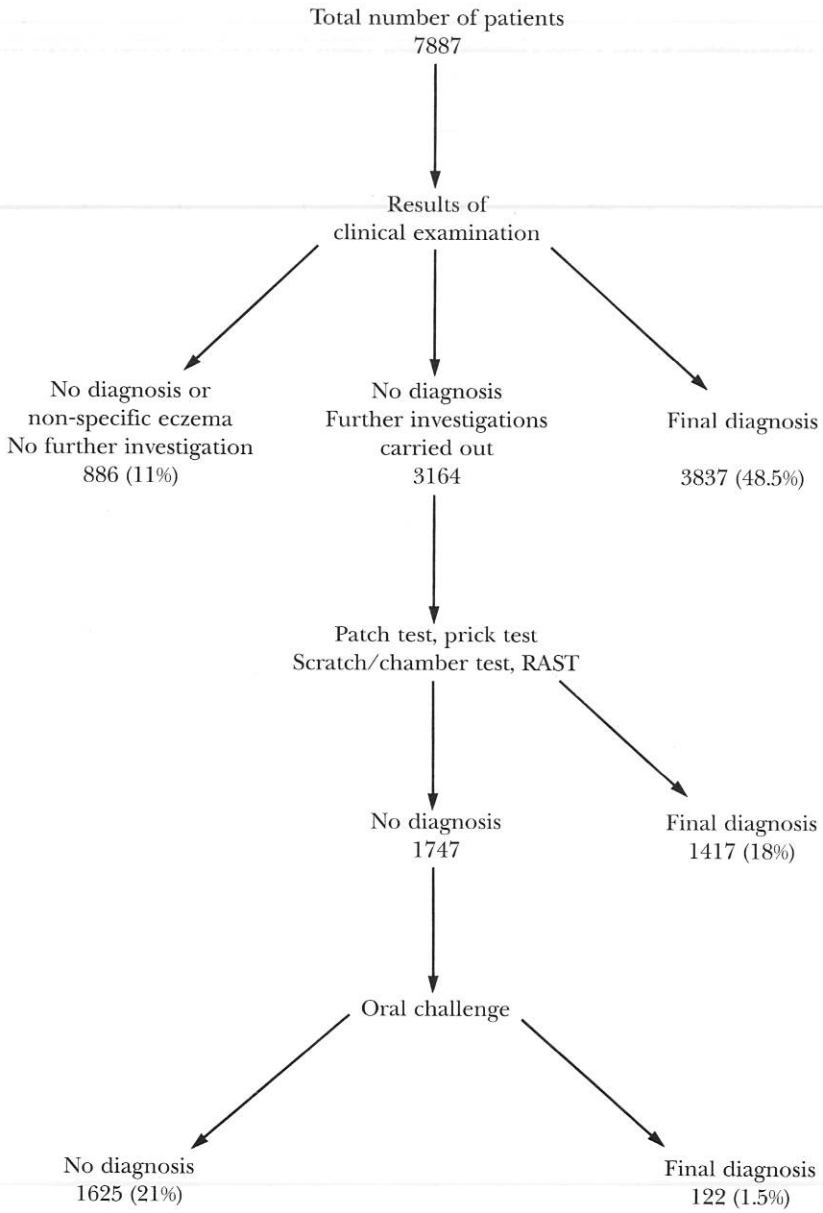
284 of 618 patients had one or more positive prick test. These tests were of diagnostic significance for 86 patients, most commonly among those with contact urticaria/protein contact dermatitis. Although prick tests and scratch-chamber tests were of limited value as diagnostic tests, they did provide some useful information about aggravating factors, particularly among patients with atopic dermatitis.

Positive oral challenge results were most commonly seen after challenge with nickel and balsam of Peru and were more common among patch test positive patients (30% of 257 tested) than among patch test negative patients (19% of 629 tested).

The oral challenge applied as a diagnostic test in patch test negative patients gave a low yield of positive reactions seen in relation to the total number of patients with eczema and considering the number of patients tested using a relatively complicated procedure. This procedure is therefore only warranted for selected patients with long-standing dermatitis which has proven refractory to traditional treatment.

The overall results of the various diagnostic procedures are given in Figure 2.

Figure 2:



Results of diagnostic procedures followed for 7887 patients with eczema.

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The results of restrictive diets

A sub-population of 675 of the 7887 patients was placed on diets to restrict the intake of metal salts, balsams or food allergens in genuine foods (Veien et al., 1987c). Each patient was seen after a period of 1 to 2 months of following the diet, and at this time the dermatitis of 262 had improved.

144 of 206 or 70% of patients (95% confidence limits 64-76%) who responded to a questionnaire follow-up had long-term benefit from the diet treatment. 11 patients stated that they could regulate the severity of their dermatitis by following a more or less restrictive diet. Atopic patients were seen to benefit more frequently than non-atopics (41 of 50 compared with 80 of 126, ($\chi^2 = 5.71$, $p<0.05$).

The fact that there was a predominance of atopics among those who benefited from the diet treatment could indicate that these patients had variants of atopic dermatitis. However, the patients in the current study commonly presented with recurrent vesicular hand eczema, and although previously linked to atopy (Menné, 1983a), this type of dermatitis is not among the classical manifestations of atopic dermatitis (Hanifin and Rajka, 1980).

Discussion

Oral challenge

Substances

The particular substances used for the challenge procedures in the studies described here (**II,V,X,XI**) were chosen either because they frequently give rise to positive patch tests upon routine testing or because they are commonly mentioned as causes of adverse reactions to foods.

Many other substances could have been implicated. Parabens in topical medicaments and cosmetics occasionally cause allergic contact dermatitis. Similar compounds are used as preservatives in food and may cause flares of dermatitis following oral challenge (Kleinhaus and Knott, 1973). Schorr, (1972) however, did not consider parabens in food to be a clinical problem.

Cross sensitivity among various p-amino compounds like azo-dyes, p-phenylene diamine, sulphonamides and saccharin could account for eczemas from foodstuffs as suggested in some case reports (Roeleveld and van Ketel, 1976; Gordon, 1974). One systematic study of the cross reactivity of some of these substances did not support the case reports; in particular, the reactivity to saccharin was found to be doubtful (Angelini and Menighini, 1981).

Methods

The test method employed in the papers upon which the current study is based was crude in the sense that it was a single dose challenge and that, where nickel was concerned, a non-physiological dose of an inorganic metal salt was used. For challenge with balsam of Peru a complex, poorly defined substance was used. Since one of the purposes of this study was to evaluate practical methods suitable for routine use, the single dose challenge was maintained.

The number of placebo reactions in the various placebo-controlled studies carried out demonstrates the importance of this type of study. Ideally, challenges should be repeated, preferably at home in familiar, every-day surroundings.

Due to limited knowledge of the bioavailability of the test substances, these should be given in a standardized way. We asked the patients to ingest the sub-

stances between meals with water or a slice of bread.

At the time of challenge the dermatitis should be stable and preferably quiescent. We have found that the patients we wish to challenge very rarely are completely free of dermatitis.

In our initial studies the determination of whether or not a flare had taken place after the oral challenge was made by combining a careful evaluation of photographs and the opinions of both patient and physician. Once experience had been gained and the use of randomized, placebo-controlled challenge procedures was routine, accepting the opinion of the patient became the most practical way of determining whether aggravation had, in fact, taken place.

No severe untoward reactions were seen in any of the challenge studies although challenge with chromium caused transient abdominal discomfort in a few patients. With this in mind, the oral challenge procedure may be considered safe for routine use.

Patients

The patients selected for the tedious challenge experiments and/or elimination diets all had long-standing, treatment refractory dermatoses of morphologies commonly considered to be endogenous. These included symmetrical, recurrent vesicular hand and/or foot eczemas, symmetrical axillary eczemas and anogenital eczemas, some symmetrical nummular eczemas and eyelid eczemas.

A total of 1310 patients were included in the oral challenge studies presented here. 628 of these had hand eczema, and 388 had hand eczema of the recurrent vesicular variety. Such patients are common. In one dermatology department patients with recurrent vesicular hand eczema constituted approximately 11% of all first consultations (Thelin and Agrup, 1985).

Recurrent vesicular hand eczema is eruptive in nature and presents with deep-seated vesicles, 1 to 2 mm in diameter, on the palms or the palmar aspects or the sides of the fingers and occasionally also around the nails. The vesicles are often severely pruritic at the time of eruption, but the skin is rarely inflamed at this stage. Confluence of the lesions is occasionally seen, and large, elevated lesions, or even bullae, may develop. Although it is less common, plantar skin may also be affected together with the palmar aspects or alone, and when afflicted, typically involves a sharply defined central area of the sole. Initial eruptions of vesicles usually heal through several stages of scaling, leaving smooth, normal skin. Repeated eruptions at short intervals together with scratching and contact with irritants and allergens will often turn a purely vesicular eruption into chronic hand eczema.

In a review of pompholyx Menné and Hjorth (1983) concluded, as had Shelley (1953), that there is still insufficient information about the etiology of recurrent vesicular hand eczema. Aside from the vesicular eruptions of the hands seen as

reactions to oral challenge with the hapten in patients with positive patch tests to medicaments and metals, these authors stressed the lack of association with the sweat glands and the fact that there may be an association between pompholyx and atopy.

Schwanitz (1986) found many smokers in his group of patients with dyshidrosis and discussed the possible significance of irritants in sweat and functional hyperhidrosis in the involved areas. Edman (1988) also found an association between vesicular hand eczema and smoking, as well as an association between this type of dermatitis and the intake of acetylsalicylic acid and oral contraceptives.

It should be stressed that vesicular hand eczema is a non-specific reaction pattern which can also result from external contact with the hapten in patients with allergic contact dermatitis and protein contact dermatitis (Schorr, 1972).

Nickel is excreted in sweat, and allergic nickel contact dermatitis could be a result of the relatively high concentration of nickel left on the skin surface when the water evaporates. Schwanitz (1986) found increased transepidermal water loss among his patients with vesicular hand eczema and found vesicular eczema to be more common on the hands than on the feet. Other factors reported to aggravate vesicular hand eczemas, such as psychological stress and premenstrual strain, might also, indirectly, be sweat related.

Other clinical features seen in patients with systemic contact dermatitis include the flares at previous patch test sites seen after experimental oral challenge but not after "spontaneous" fluctuations in the dermatitis. In addition, there can be a generalized rash which is most predominant in flexures, on the eyelids and in the ano-genital area (baboon syndrome) and vasculitis of the legs and on the extensor side of the forearm (Hjorth, 1976; Andersen KE et al., 1984; Menné, 1983b).

Diet instructions

Prior to the diet trials, various diet instructions were compiled. We received assistance from dieticians only for the solving of specific problems. Questions concerning malnutrition can be answered more readily, and more detailed restrictive diets compiled, with the assistance of a trained dietician. This is particularly important when dealing with children.

Diets with reduced nickel or balsam content should present no problems with regard to malnutrition although this can be of concern when attempting to restrict ingestion of other substances such as chromium and cobalt.

Prior to the initiation of an elimination diet, it can be helpful if the patient has compiled a diet diary listing the foods commonly ingested. We have found such diaries more useful in treating patients with urticaria or other types of immediate reactions, however, than for patients with eczema, which flares and fades much

more slowly.

The instructions for reducing nickel intake given here were made to suit traditions prevalent in Denmark and are therefore subject to adjustment according to local eating and drinking habits.

Since it is difficult to adhere to a restrictive diet and because such a diet disrupts the normal social life of the patient, it should be suggested only for patients with long-standing disease which has proven refractory to traditional therapy. For this reason diet instructions should be as unrestrictive as possible. Follow-up consultations should be arranged and diet treatment discontinued if such therapy fails to result in improvement of the dermatitis within 1 to 3 months.

It is important to seek methods other than restrictive diets to eliminate substances which cause systemic contact dermatitis. Chelation therapy appears to be effective for some nickel allergic patients, but hepatotoxic side effects have been seen in an appreciable number of patients. Antabuse® is therefore not suited for the routine treatment of systemic nickel contact dermatitis (Kaaber et al., 1987). The successful induction of immunological tolerance by the repeated oral administration of nickel to nickel allergic patients was recently described by Sjövall et al. (1987).

Conclusions

Placebo-controlled, single-dose oral challenges with nickel, cobalt, chromium and balsam of Peru are practical and safe procedures in patients with eczema.

The oral challenge procedure gives a high yield of reactions in patients with positive patch tests to nickel, cobalt, chromium and balsam of Peru when these patients are challenged with the substance to which they had a positive patch test. Patch test negative eczema patients are also seen to react to oral challenge with these substances, but this is less common than in patch test positive patients.

In a general dermatological practice the number of eczema patients for whom the final diagnosis is made by means of oral challenge procedures is low compared with other diagnostic measures.

It is possible to reduce nickel intake by half by adhering to a diet of foods with low nickel content.

Depletion diets are helpful for approximately half of the patients who have certain types of eczema and positive patch tests to nickel as well as for patients with negative patch tests who experience aggravation of their dermatitis after oral challenge with nickel. A restrictive diet generally improves, but does not cure the dermatitis.

Future aspects

It would be useful to study more differentiated oral challenge procedures and to make comparisons between single and multiple doses of the challenge substances and among various chemical compositions of the challenge substances.

The bioavailability and homeostasis of the substances suspected to cause systemic contact dermatitis, such as nickel, cobalt, chromium and balsam of Peru, should be studied in greater detail. Oral challenge studies with the individual components of balsam of Peru as well as with commonly used spices and/or artificial flavorings and other food additives should also be carried out.

Placebo-controlled oral challenge studies with genuine foods should be carried out.

Controlled depletion diet trials would be valuable.

The etiology and pathogenesis of recurrent vesicular hand eczema should be

studied with emphasis on studies of immune functions including immune complexes in the eczematous lesions themselves.

Resumé

Formålet med denne oversigt var at belyse, om alment forekommende kontaktallergener som nikkel, kobolt, krom og balsamer kan være årsag til systemisk induceret kontaktdermatitis, og om indtagelse af levnedsmiddeltilsætningsstoffer kan forværre tilsvarende eksemtyper.

En undersøgelse af 144 patienter med positiv nikkel og/eller koboltlappeprøver, som fik foretaget dobbeltblind, peroral provokation med 2,5 mg nikkel, 1 mg kobolt og placebo viste, at 55 af 131 med positiv nikkellappeprøve reagerede på nikkelprovokationen, mens 23 havde placeboreaktioner ($p<0,001$). 28 af 47 med positiv koboltlappeprøve reagerede på kobolt, mens 5 reagerede på placebo ($p<0,001$).

Ved placebokontrolleret peroral provokation med 2,5 mg krom givet som kaliumdikromat forværredes eksemet hos 11 af 31 kromatallergiske patienter. Hos 9 af 14 med recidiverende vesikuløst håndeksem forværredes eksemet efter provokationen sammenlignet med forværring hos 2 af 11 med andre eksemtyper.

Ved peroral provokation med såvel nikkel som kobolt og krom hos eksempatienter med negative lappeprøver sås hos 58 af 202 (29%) patienter med recidiverende, vesikuløst håndeksem reaktion på ét eller 2 af metalsaltene. Der var hos kvinder typisk reaktion på nikkel, mens mandlige patienter typisk reagerede på krom.

Kostomlægning med reduktion af nikkelindtagelsen førte hos patienter med positive nikkellappeprøver og/eller reaktion på peroral provokation med nikkel til, at 121 af 204 patienter havde reduceret eksemintensitet efter 1-2 måneder. En spørgeskemaefterundersøgelse 1-5 år efter behandlingens påbegyndelse viste, at 88 (59% af de 150, der blev opnået kontakt med; 95% sikkerhedsgrænse 50-67%), havde god langtidsvirkning af kostomlægningen.

Baseret på måling af nikkelindholdet i en række levnedsmidler blev en revideret instruktion til brug ved kostomlægning hos nikkelallergikere udarbejdet.

Hos 8 frivillige forsøgspersoner måltes en indtagelse af nikkel på gennemsnitlig 0,13 mg pr. døgn, mens de indtog normal kost, mens døgnindtagelsen var 0,07 mg, når de samme personer fulgte den reviderede nikkelkostinstruktion ($p<0,01$). Ved bevidst indtagelse af kost med meget nikkel var døgnindtagelsen gennemsnitlig 0,25 mg, hvilket var signifikant mere, end mens forsøgspersonerne indtog normal kost ($p<0,05$).

Placebokontrolleret, dobbeltblind peroral provokation med 1 g perubalsam førte til eksemforværring hos 10 af 17 patienter med positiv lappeprøve for perubalsam (1 reagerede på placebo) ($p<0,05$), og hos 12 af 58 med recidiverende vesikuløst håndeksem og negative lappeprøver (3 reagerede på placebo) ($p<0,05$).

Placebokontrolleret, dobbeltblind, peroral provokation med en gruppe levnedsmiddeltilsætningsstoffer hos 101 patienter med eksem, hos hvem levnedsmiddeltilsætningsstoffer formodedes at være eksemårsagen, viste ikke statistisk forskel mellem hyppigheden af reaktion på aktivt stof og placebo.

Prospektiv registrering af diagnoserne hos 7887 konsekutive patienter med eksem viste, at den endelige diagnose blev stillet klinisk hos 48,5%, mens den hos andre 18% blev stillet, efter at der var udført diagnostiske kutantests, væsentligst i form af lappeprøver. Peroral provokation førte til en endelig diagnose hos 1,5% af patienterne.

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Appendix

Diet instructions for the reduction of nickel intake

It is not necessary to restrict intake of the following foods:

Meat, fish, etc.

All kinds of meat and poultry
fish
eggs

Dairy products

Butter,
cheese
milk in all forms
yoghurt (unflavored)

Vegetables

Asparagus
beets, red
broccoli
Brussels sprouts
cabbage, white
cauliflower
Chinese cabbage
corn
cucumber
dill
egg plant
mushrooms
parsley
peppers, green, red
potatoes

The following food items have a high nickel content:

Meat, fish, etc.

Shellfish like shrimp and mussels

Dairy products

None

Vegetables

Beans (green, brown, white)
kale
leeks
lettuce
peas
spinach
sprouts made from beans and lucerne

Grains and grain products

Breakfast foods made of rice
cornflakes
macaroni
popcorn
rice (white)
spaghetti
wheat flour
whole grain rye and
wheat bread *in moderation*

Buckwheat
millet
oat meal
wheat bran, i.e. bran and
fiber products incl. cereals
bran bisquits, fibre
tablets
multi-grain breads

Fruit, berries, etc.

Peaches
pears
raisins
rhubarb
all berries *except*
raspberries

Figs
pineapple
prunes
raspberries

Drinks

Coffee and tea (not too
strong and in moderation)
soft drinks
alcoholic beverages
(destilled products and
drinks made from these)

Chocolate and cocoa drinks
Tea from drink dispensers

Miscellaneous

Margarine
yeast

Almonds
baking powder (in large amounts)
hazel nuts
lentils
linseed
peanuts
soy protein
sunflower seeds
sweets containing chocolate,
marzipan, nuts, strong
licorice
vitamins containing nickel

(cont.)

Various other food items and drinks can aggravate nickel eczema even though the nickel content of these foods may be low. Included among these are beer, wine (in particular red wine) herring, mackerel, tuna, tomato, onion, carrot and certain fruits, in particular, apples and citrus fruits (juice). The vegetables mentioned here can usually be tolerated when cooked.

The first liter of water taken from the tap in the morning should not be used in food preparation, as nickel may be released from the tap during the night. Nickel-plated kitchen utensils, such as egg beaters and tea balls, should be replaced.

Acid foods such as stewed fruits and rhubarb cooked in stainless steel utensils should be avoided. The acids in the foods can cause nickel to be released from the utensils. Tinned foods should be eaten only in moderation.

Although your eczema is probably mostly due to the intake of foods containing nickel, it should be pointed out that prolonged physical contact with nickel-plated items can make it worse.

It is important to follow the diet instructions for at least 1 to 2 months. It can be difficult to change eating habits for a long period of time, and it is therefore recommended that you adhere to the instructions as closely as possible when eating at home. When eating away from home, the diet can be modified as necessary.

The eczema will not necessarily clear during the diet period, but there will ordinarily be fewer and shorter flares, and these will gradually diminish in intensity.

If, after 1 to 2 months, the diet seems to have had good effect, it is recommended that you continue for 6 months to a year to eat only moderate amounts of those foods with a high nickel content.