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ECZEMATOUS ALLERGY TO METALS¹

By

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1. RANGE AND DEFINITION

Positive patch-tests to metals or metal salts are demonstrable in about one-third of all cases of allergic eczematous dermatitis of the contact type. This conception based on experience in the Finsen Institute through 23 years (Table 1) is not far from the previous estimates of *Gaul* (35, 36) and of *Thyresson & Skog* (105). Comparison with many statistics on this subject is difficult, because the population groups examined and the techniques used have differed and especially because a definition of the metal salts used for testing is very seldom given, even in text books (4, 33, 85, 91, 107). Nearly all commercially available metal salts are contaminated with other metals in varying often considerable amounts. I shall prefer to define metal allergy as *eczematous* allergy to metals, simple salts of metals and a few chemicals which behave in the same way, e.g. chromic acid salts.

2. INCIDENCE IN OCCUPATIONAL AND EVERYDAY LIFE

The use of metals is so closely connected with technical progress that a steady rise in metal allergies was expected, most marked in occupational dermatitis caused by exposure to strong solutions of metal salts. *Schwartz, Tulipan & Birmingham* (91), however, consider metal allergies unimportant. A comparison of the comprehensive material of *Schwartz* (89)

¹ An extract was presented to the XII International Congress of Dermatology, Washington, 1962.

with the cited material of mixed dermatitis from the Finsen Institute (Table 2) shows a percentage of allergic metal dermatitis among panel patients exceeding the sum of primary irritant and allergic metal dermatitis in industry. Comparison of the two materials must be permissible, because metal industry is extensive in the U.S. and negligible in Denmark. For nickel allergy alone a similar distribution was demonstrated as early as 1929 by *Jadassohn & Schaaf* (51) and confirmed by *Hunziker & Musso* (48) in 1960 at a time when *Calnan*, (14) *Fisher & Schapiro* (30) and *Marcussen* (60) demonstrated that nickel allergy was an important problem in everyday life. The explanation is possibly that industrial medicine solved the problem even before the concept occupational allergy was recognized (*Bulmer & Mackenzie* 1926 (12)). The fate of the eczematous allergy to Beryllium described by *Curtis* 1951 (17) is a further proof of the efficiency of industrial medicine.

TABLE 1

	No. of patients with dermatitis	Per cent of tested persons	Per cent of positive reactors
Routine patch tests	43.502		
Positive reactions to one or more patch tests	11.706	(26.9)	
Positive reaction to metal salts	3.828	8.8	32.7

Cases of dermatitis submitted to routine patch tests in The Finsen Institute 1938 to 1960.

TABLE 2

	41.628 Occupational dermatitis (Schwartz 1955)	43.502 All types of dermatitis (The Finsen Institute 1938-60)
	Primary irritant and allergic per cent	Allergic only per cent
Metal and Metal plating	6,0	6,3
Chromates and Chromic acid	1,7	2,5
	7,7	8,8

3. INCIDENCE CURVES

The incidence of metal allergies should thus preferably be studied in the dermatological clinics. Systematic studies of this kind are few, but most authors agree on the point that mercury, nickel, chromic acid salts and cobalt are the only metals responsible for allergies of major extent.

TABLE 3
Cases of less common metal allergy reported in recent literature.

Metal	Author	No. of cases
Copper and brass	Becker and O'Brien (5)	8
	Epstein (23)	14
	Gaul (35)	4
	v. d. Meer (63)	1
	Morris (70)	5
Gold	Cowan (16)	1
	Forster and Dickey (31)	1
	Gaul (36)	1
Iron	Nater (72)	1
Platinum and Iridium	Sheard (93)	1
Silver	Gaul (36)	1
Zinc	v. d. Meer (63)	1

For most of the common metals to whom everybody is equally exposed no cases of allergy have been reported. I have listed most of the cases reported in the last 10 years (Table 3). Apart from some reactions to copper, they consist of 7 cases of positive patch tests, some in Patients with definitely proved allergic dermatitis.

The following incidence curves from the Finsen Institute are based on routine patch tests on all cases of dermatitis. We have a certain control of their relevance, because the country has no mining and no metal refining industry. The metals are

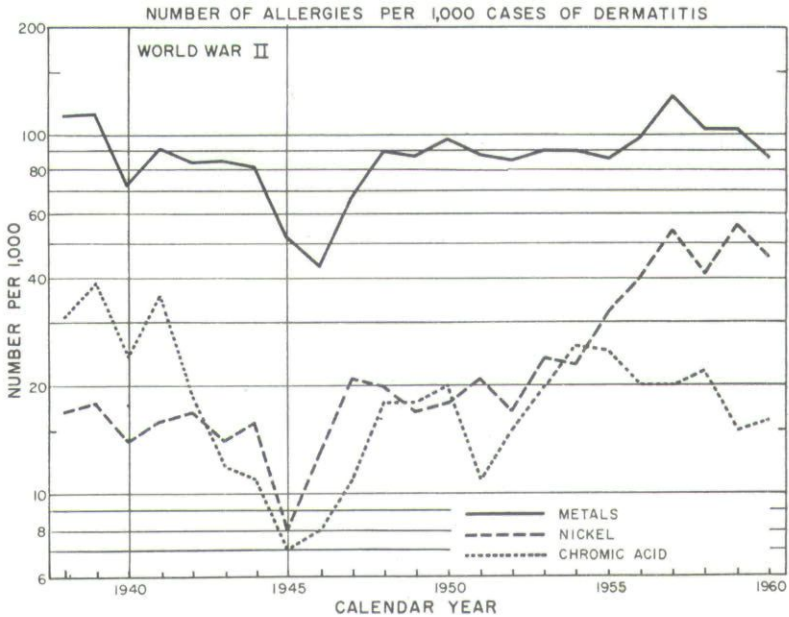


Fig. 1.

imported in a known quantity, and the curve of nickel allergy roughly follows the imported quantity of nickel (60).

Our total of metal allergies (Fig. 1) showed a fall from 11 to 4 per cent during and after World War II, during which importation stopped and did not return to pre-war level until 1957. The incidence of nickel- and chromate hypersensitivity is mainly responsible for this course. Analysis of representative years confirmed that nickel dermatitis is a result of wearing nickel on the skin (Fig. 2) and the curve is rising, while chromic acid dermatitis is occupational and the incidence lower than before the war (Fig. 3). Möbest (71) has registered a rising incidence. The incidence curve for mercury showed a peculiar, irregular course (Fig. 4) with a falling tendency due to the therapeutic use of mercury. In 1960 it could be characterized as an immunologic scar in the population, and this was supported by the fact that mercury allergy was found mainly in old people and in long-standing cases of dermatitis. The incidence

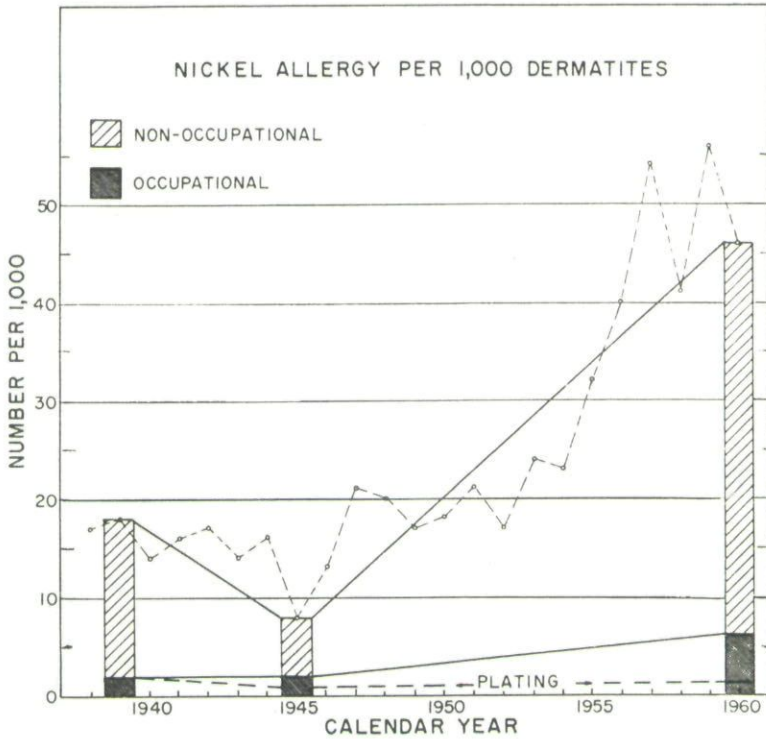


Fig. 2.

curves of the main metal allergies thus seem to be determined by well-known ecological factors and completely unrelated, except when the metals are withdrawn from the population.

4. RELATIONSHIP BETWEEN METAL ALLERGIES

It is a well known fact that some individuals present a reaction to more than one metal salt. *Stewart* (100) was the first to suggest that this was a cross-sensitivity, and extensive work has been done to support or disprove this theory. These investigations are well known (Table 4), and a fascinating review of this question, based on the approximate localization of the metals in the periodical system of *Antopoff*, was recently published by *Storck & Schwarz* (102). *Rostenberg & Perkins* (84)

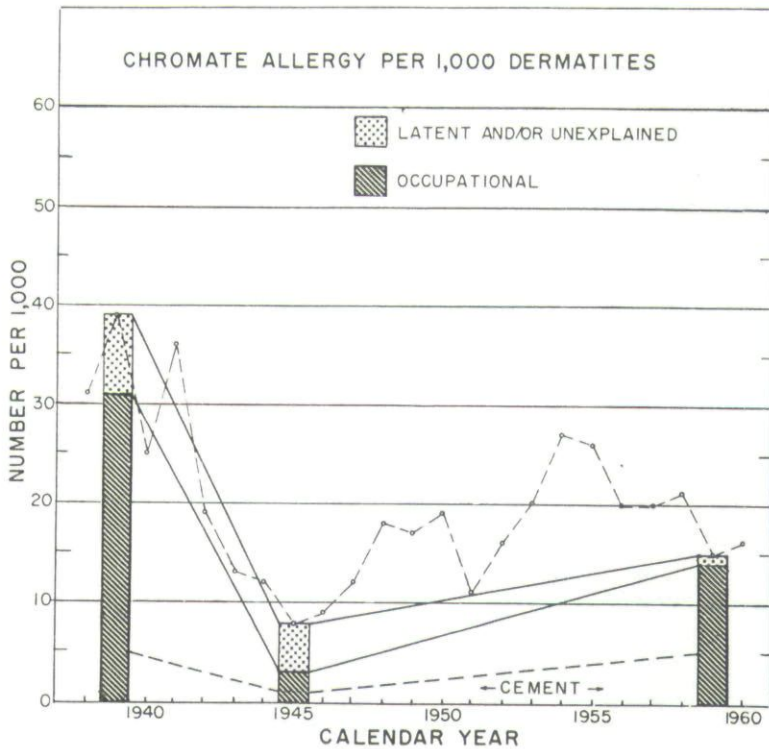


Fig. 3.

and Schwartz, Tulipan & Birmingham (91), however, have pointed out the pitfalls involved by double exposure during sensitization and testing with commercial chemicals. In fact, no person is exposed to a pure metal and no person is tested with a completely pure chemical. The relationship may thus be explained in the nomenclature of Baer (3) as multiple primary specific sensitivity. The question of sensitization from trace elements first suggested by Jaeger & Pelloni (52), and the high reactivity to tests differing from the patch test, especially intradermal tests, have greatly complicated this problem.

We can make an approach from different sides. Estimating the co-incidence of reactions in groups of more than one thousand positive patch tests (Table 5), the coincidence of nickel

and chromic acid is somewhat higher than the average, but after correction for verified occupational double exposure, it decreases to close to the average. The clinical findings in a consecutive series thus give no support to a cross-reaction between nickel and chrome.

TABLE 4
Theory of Cross-sensitivity between Metals.

	Authors pro	Authors contra
Nickel - Cobalt	Stewart (100) Haxthausen (42) Gaul (36) Everall, Truter and Truter (25) Epstein (24)	Rabeau et Ukrainzyk (79) Rostenberg and Perkins (84) Fisher and Shapiro (30) Zina e Bonu (118)
Nickel - Copper	Epstein (23)	
Nickel - Chrome	Everall, Truter and Truter (25)	Pirilä (77) Zina e Bonu (118)
Chrome - Cobalt	Everall, Truter and Truter (25)	Pirilä (77) Geiser, Jaenneret et Delacretaz (39)

TABLE 5
Coincidence of Nickel and Chrome Allergy.

Positive patch test to Nickel and/or	Positive patch test to both	Per cent
Primrose 2188	43	1,9
Turpentine 1458	15	1,1
Bals. of Peru 1368	14	1,1
Colophony 1181	16	1,4
Chromate 1307	43	3,3
Average		1,7
Chromate* 1289	25	1,9

* corrected for 18 cases of verified occupational double exposure (chemical and plating industry).

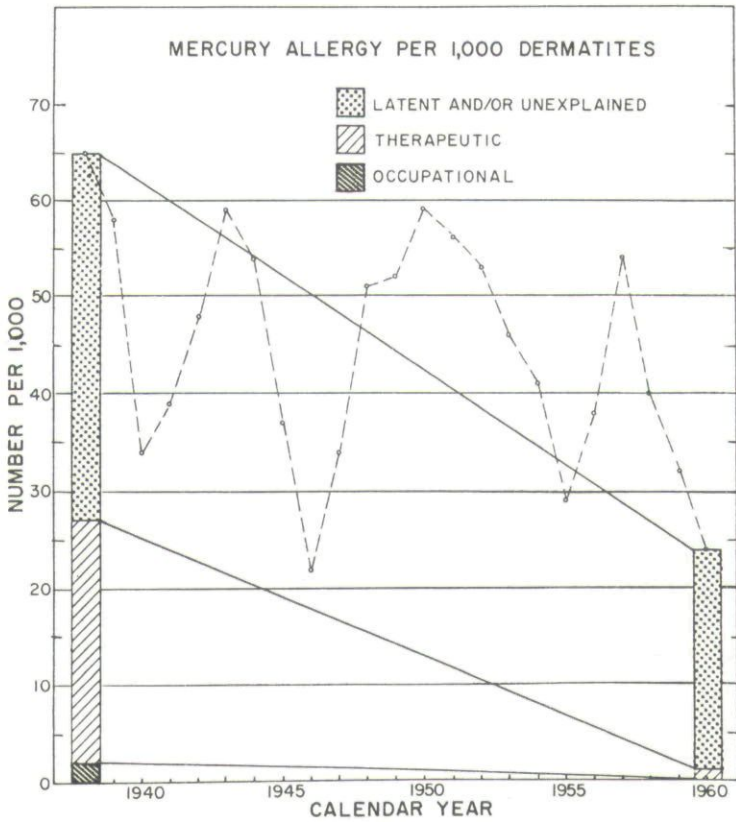


Fig. 4.

Another approach is to estimate the value of tests using more or less metal-contaminated test solutions. I have determined the reactivity of a group of cobalt negative nickel allergies to patch test and intradermal test with a nickel sulphate¹ containing only 0.0005 per cent cobalt (Fig. 5). If you test the same group with a technical cobalt chloride, the patch test may be positive in 5 per cent, and the intradermal test in 90 per cent. The best analytical cobalt chloride² with a nickel content of

¹ Nickel sulphate 'AnalaR' BDH. (Co < 0.0005 %).

² Cobaltum chloratum pro anal. Merck (N: < 0.005 %).

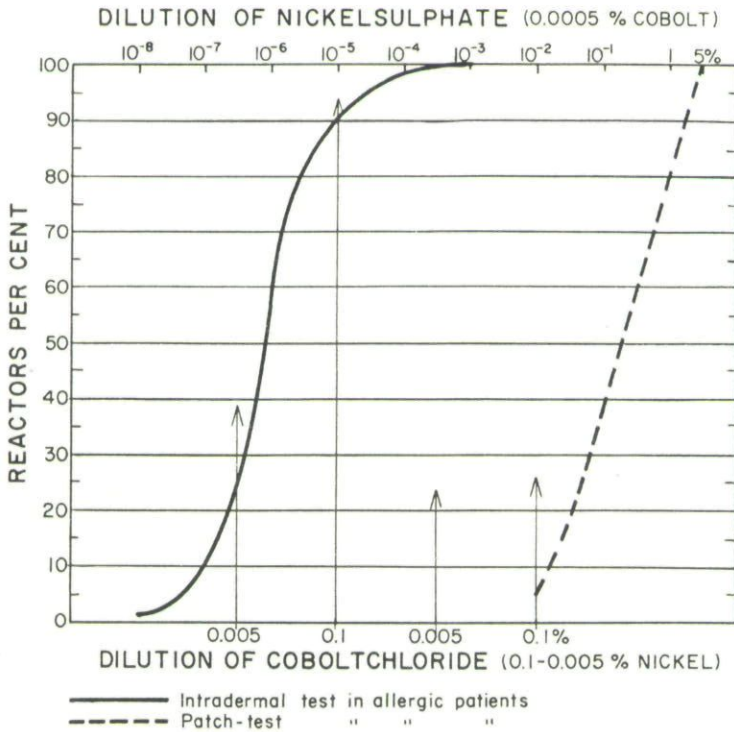


Fig. 5.

0.005 per cent will possibly give no positive patch tests but 25 per cent positive intradermal test.

5. INTRADERMAL TESTS

Epstein's (24) introduction of the intradermal test is one of the most important steps in the study of metal allergies. Having used a standardized intradermal test for several years, I am in a position to confirm that a dilution of 1:10,000 nickel sulphate gives a positive reaction in clinical nickel allergy and no reaction in controls in whom cobalt allergy has been excluded. Fig. 6 gives the reactions to intradermal tests in nickel allergies and controls and the reactions to patch tests with nickel sulphate in nickel allergies. The criterion of isolated

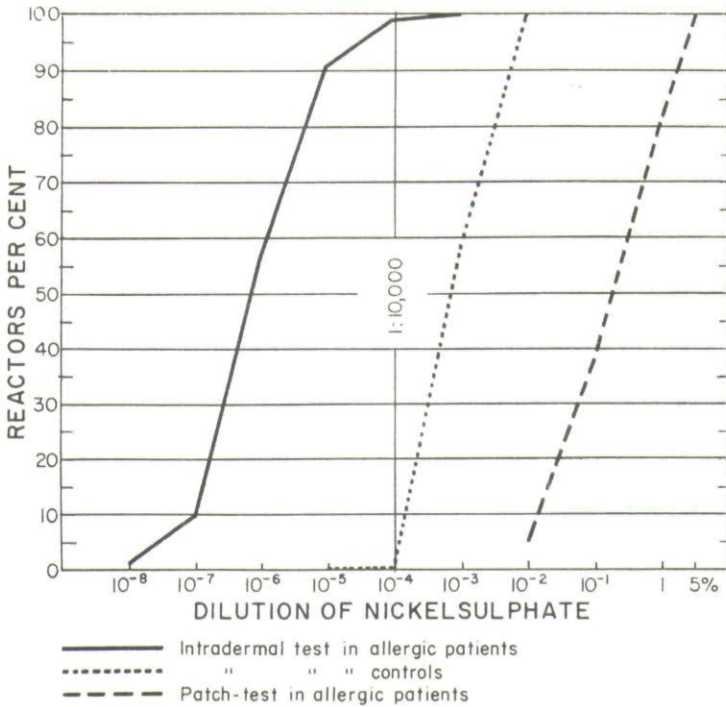


Fig. 6.

epidermal allergy advanced by *Epstein* (24): a positive epidermal test and a negative intradermal test with the same dilution of nickel sulphate, can apparently never be fulfilled, because the dilution of nickel sulphate which give positive patch tests in nickel-allergics are bound to give positive intradermal tests in nickel allergics as well as controls.

I have so far had no opportunity to see a case of reproducible epidermal reaction when the intradermal test was negative. The isolated intradermal reaction is on the other hand an impressive fact. In agreement with *Rostenberg* (82, 83) I do not feel convinced that this is a special form of sensitivity, it is my impression that the intradermal test reveals cases of weak hypersensitivity, not demonstrable by the patch test. I think *Epstein's* (24) investigations will finally correct an old mis-

interpretation of the early experiments of *Jadassohn* (50) and *Blumenthal & Jaffé* (8). For 30 years dermatology has been making its diagnostic tests outside the protective coat of the skin. I think that experiments with abrasive, alkali, stripping, pressure and intradermal tests all tend to show that perhaps the conventional patch test is not always sufficiently sensitive (*Kvorning & Borup Svendsen* (55), *Samitz & Pomerantz* (88), *Spier & Sixt* (98), *Fernström* (26,27)).

6. DEGREE OF SENSITIVITY IN METAL ALLERGY

The intradermal test has demonstrated a very high degree of reactivity in metal allergy. In nickel allergy reactions may be evoked by dilutions of from 1:10,000 to 1:100,000,000. In chromic acid allergy *Hercus & Purves* (43), as early as 1935, demonstrated sensitivity to chrome in amounts so small as to be far beyond the limits of chemical analysis.

7. SENSITIZATION BY TRACE ELEMENTS

It is generally accepted that experimental sensitization of the skin requires a certain concentration of the antigen (*Miescher* (66)). *Jaeger & Pelloni* (52), however, have demonstrated that very small amounts of chromium in cement must be responsible for a high percentage of the cement eczemas, and this has been confirmed by important investigations from several countries (Table 6). Moreover *Anderson's* (1) experiments indicate that the production of dermatitis may not be quantitatively related to the amount of chromium taken up by the skin. *Kroepfli & Schuppli* (53) and *Krüger & Dorn* (54) have pointed out the importance of chromium traces in detergents, *Freger* (32) in matches, *Anderson* (2) in rustpreventives, *Rabeau & Ukrainzyk* (80), *Samitz* (86, 87), *Bernhardt* (7) and *Bockendahl* (9) in other unexpected locations. In some cases a positive patch test may be obtained by an extract of cement, but it is characteristic that other test methods, including scratch, abrasio, stripping, intradermal and various moist

TABLE 6
Per cent of positive reactions to chrome in cement dermatitis.

Year	Author	No. of patients	Positive patch test to chrome
1950	Jaeger et Pelloni (52)	32	94
1951	Peryassu, Negreiros et de Carvalho (75)		96
1952	Spier und Natzel (95)	67	65
	Engelbrecht (22)	32	65
	Frey (34)	33	88
	Engelbriksen (21)	8	100
	Meneghini (64)		77
	Bonnevie (11)	7	71
	De Carvalho et Negreiros (78)	30	96
1954	Ramos e Silva (81)	45	93
	Denton, Keenan and Birmingham (20)	7	60
	Pirilä (77)	90	82
	Wilt (45)	14	71
1955	Leihancová und Wolff (56)	28	73
1956	Zina (117)	139	72
1959	Darabos und Fylöp (19)		65
1960	Hunziker et Musso (49)	112	92
	Geiser, Jaenneret et Delacretaz (39)	53	92
	Anderson (2)	66	95
			60-100

TABLE 7
Test procedures diverging from the classical patch test used to demonstrate chrome allergy in cement dermatitis.

Year	Author	Type of skin test			
		Alkali-buffer	Scarification	Strip	Intra-dermal
1953	Sidi et Longueville (94)		+		
	Spier und Natzel (96, 97)	+		+	
1955	Miescher, Amrein und Leder (67)	+			
	Leihancová und Wolff (56)	+			
1957	Marson e Galla (62)				+
1958	Charpy, Calas, Privat et Bourhis (15)		+		
1960	Behrbom (6)		+		
	Darabos (18)	+			+

(*Gaul* (37)) and alkali tests have been utilized with better results (Table 7). A common feature of these tests is that of increasing the passage through the protective coat of the skin, removing, or by-passing it.

I think we must accept not only that a very high degree of sensitivity is present, but also that this is not always demonstrable by the classical patch test procedure, and finally that a sensitization and maintenance of a dermatitis may be due to very small amounts of chemicals. Chromic acid is a very good sensitizer (46, 57, 74, 109, 113). Nickel is perhaps not an equally good sensitizer (40, 47, 51, 68, 74, 88, 101, 110). Furthermore nickel very probably has difficulties in penetrating the epidermal layer apart from the follicular openings (*Wells* (112), *Magnus* (59)). Stripping highly increases the reactivity (*Spier & Sixt* (98)) and alkali increases the sensitizing ability, as demonstrated by *Burckhardt* (13) and *Haxthausen* (42). Although it has not been proved directly, it seems very probable that quite small quantities of nickel are able to sensitize and that microtraumas (*Schwartz, Peck, Blair & Markuson* (90), *Schwarz & Spier* (92) from hard metal objects should not be under-estimated. According to *Haxthausen* (42) and *Pirilä* (76) cobalt seems to be a most successful sensitizer. The idea, which seems to have been advanced by *Pirilä* (77) and *Geiser, Jaenneret & Delacretaz* (39), that cement eczema may be induced by cobalt traces is, therefore, reasonable. Cobalt also seems to be a better sensitizer than nickel (*Haxthausen* (42)). It should be remembered that the approximate position of nickel and cobalt in the atomic table virtually makes it impossible to find one of these metals without contamination by the other.

If trace elements are able to cause sensitization, and if cobalt is a better sensitizer than nickel, it might be possible to find cases where cobalt hypersensitivity is responsible for the very typical clinical picture hitherto described as nickel dermatitis. In a comprehensive group of dermatitis caused by nickel alloy I have succeeded in finding 3 cases of dermatitis caused by metal worn on skin but reacting only to cobalt (Table 8). Such

cases indicate that hypersensitivity to nickel and cobalt may be explained without assuming cross-reactivity and may explain some of the false negative reactions in nickel allergy (*Bonnevie* (10)).

TABLE 8
Presumed nickel dermatitis found to be caused by cobalt.

Patch test	Nickel sulphate (Co < 0.0005 %) 5 % 0	Cobalt chloride (Ni < 0.005 %) 2 % ++
<i>Intradermal test</i>	Nickel sulphate (Co < 0.0005 %)	Cobalt chloride (Ni < 0.005 %)
Dilution		
10 ⁻²		29 mm
10 ⁻³		25 mm
10 ⁻⁴	0	13 mm
10 ⁻⁵		9 mm
10 ⁻⁶		Erythema
10 ⁻⁷		3 mm
10 ⁻⁸		0 mm
Control	0	0 mm

Case No 255432 Female 54 years
Dermatitis from brassiere buckle.

8. THE FOLLICULAR PATCH TEST REACTION

The follicular reaction was described by *Steiner* (99), but its problems have been investigated by *Sulzberger* with *Hill* (44), *Goodman* (103) and *Witten* (104), by *Wilson* (114) and by *Fisher*, *Chargin*, *Fleischmajer* & *Hyman* (28). Most authors agree that this is a primary irritant reaction, but recently *Becker* & *O'Brien* (5) and *Epstein* (24) have interpreted it as a sign of isolated dermal allergy.

With nickel sulphate 5 per cent this reaction can be consistently evoked in children in whom specific sensitization must be out of the question. The reaction appear alone or combined with other types of primary irritant reactions, most common in babies and infants. In these infants the intradermal test (*Epstein* (24)) and the open test (*Wedroff* (111)) are nega-

tive (Table 9), and the follicular reaction *must* be a primary irritant reaction.

TABLE 9
Reactions to nickel sulphate in children 0-10 years old.

	Covered patch test (Jadassohn- Bloch) Nickel sulphate 5 %	Open test (Wedroff)	Intradermal test (Epstein) Nickel sulphate 1:10,000
Follicular reactions per cent	9	0	0
Reactions per cent	25	0	0

The investigations of *Wells* (112) and *Magnus* (59) indicate that nickel is able to penetrate the follicular openings. *Spier & Sixt* (98) have demonstrated that the horny layer is relatively resistant.

TABLE 10
*Repeated patch tests in a case of nickel dermatitis with positive intradermal test.
Result read after 48 hours.*

	Patch test Nickel sulphate 5 %	Intradermal tests Nickel sulphate 10 ⁻⁴
25' Oct.	0	23 mm
27' Oct.	0	
28' Oct.	0	
30' Oct.	follicular	
2' Nov.	+(+)	17 mm
6' Nov.	+++	
8' Nov.	+++	

Case No. 369254 Female 54 years.

Garter dermatitis. Cobalt chloride 2 % : 0.

A follicular picture may, thus, be found in cases where the reaction can be elicited only by the quantity of nickel which penetrates the follicular openings. This may occur in weak and be demonstrated in increasing allergies (Table 10) and is possibly rather the exception than the rule.

9. PERSISTENCE OF NICKEL ALLERGY

Ukrainzyk (106), *Witten & Shair* (116) and *Fisher, Pelzig & Kanof* (29) have demonstrated that eczematous allergy is extremely prolonged, and most authors agree that it is a lasting condition. This has been confirmed by recent years' investigations into nickel allergy (Table 11). In nearly all clinically verified cases allergy seems to persist. It may be weak, delayed ((*Wilson* (115), *Wagman* (108)) or it may require a higher concentration of the test-solution (*Everall, Truter & Truter* (25)).

TABLE 11
Patch tests repeated at long intervals in cases of nickel allergy.

	Interval (years)	No. of cases reex- amined	Allergy disap- peared no. of cases	Mode of verification
Morgan 1953 (69)	1.5-11	54	23	Patch test only
Nielsen and Bang 1954 (73)	2-9	11	2	
Marcussen 1959 (61)	1-17	11	9	
Everall, Truter and Truter 1954 (25)		28	(2)	Patch test and clinical evidence
Wilson 1956 (115)	0.5- 5	34	0	
Fisher and Shapiro 1956 (30)	2-17	40	4	
Marcussen 1959 (61)	1-20	27	1	
Wagmann 1959 (108)	1- 7	18	0	

CONCLUSION

Special attention should be drawn to the hypersensitivity to minute amounts of metal salts demonstrated by means of intra-dermal tests and various modifications of patch tests, all tending to remove or destroy the protective coat of the skin. This hypersensitivity is not regularly demonstrable by means of the classical patch test procedure.

In addition, it is convincingly evident that sensitization may be caused and maintained by trace elements found on micro-analysis in the patient's environment. These viewpoints differ from the earlier conception of eczematous sensitivity and sensi-

tization, and afford the explanation of a number of paradoxical results, in particular so-called cross reactions, false negative reactions, and persistence of dermatitis when the allergen has apparently been removed. Further investigations may, however, be required if these results are to be fully utilized. A standardization of the newer test techniques and a thorough comparison with the classical patch test are very important. A definition of the metal salts used for the testing, especially of their content of other metals, is hardly needed. Unlike many other biological tests, the dermatological tests are considered less conclusive. A more systematic approach to standardization might place them with the conclusive biological tests known from other fields of medicine.

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