

- scenzen der unbehandelten Lues I und Lues II. Arch Dermatol Forsch 243: 241, 1972.
5. Nazzaro-Porro, M., Passi, S., Morpurgo, G. & Breathnach, A.: Identification of Tyrosinase inhibitors in cultures of Pityrosporum. J Invest Dermatol 71: 205, 1978.
  6. Pandhi, R. K., Bedi, I. R. & Bhutani, I. K.: Leucomelanoderma in early syphilis. Br J Vener Dis 51: 348, 1975.
  7. Prabhakaran, K., Harris, E. B. & Kirchheimer, W. T.: The interaction of Mycobacterium leprae and Melanocytes in vitro. Cytobios 4: 93, 1971.
  8. Wecke, J., Bartunek, J. & Stüttgen, G.: Treponema pallidum in early syphilitic lesions in humans during high-dosage penicillin therapy. An electronmicroscopical study. Arch Dermatol Res 257: 1, 1976.
  9. Wrzolkowa, T. & Kozakiewicz, J.: Ultrastructure of vascular and connective tissue changes in primary syphilis. Br J Vener Dis 56: 137, 1980.

## Sensitization to Cobalt Associated with Nickel Allergy: Clinical and Statistical Studies

Th. van Joost<sup>1,2</sup> and J. J. E. van Everdingen<sup>1</sup>

<sup>1</sup>Department of Dermatology, Academisch Medisch Centrum, Amsterdam, The Netherlands,

<sup>2</sup>Department of Dermato-venereology, Dijkzigt Ziekenhuis, Rotterdam, The Netherlands

Received October 28, 1981

**Abstract.** In 76 cases (5.8%) of a population of 1 310 cases (examined by patch tests for possible contact dermatitis) a combined (coupled) allergy was found to nickel and cobalt. In 37 out of the 76 cases this combined allergy was associated with clinical dermatitis of the hands. Statistical chi-square analysis revealed that in the original population of patients examined, apart from a strong association between nickel and cobalt reactions, a significant association was also seen extending to the actual level (weakly to strongly positive) of reactions. Moreover this statistically significant association was still seen within the restricted population of combined nickel and cobalt allergics. Statistical association within the population of combined nickel and cobalt allergy between the strength of the Ni and Co reactions and positive reactions to other antigens of routine ICDRG-standard battery was not encountered, however. Positive reactions to cobalt were rare, but extreme. Nickel patients appeared to have about 50 times greater odds of being extreme cobalt positive. The possibility is discussed that facilitation of clinical cobalt allergy might be triggered by a high grade of nickel sensitivity.

**Key words:** Cobalt hypersensitivity; Nickel hypersensitivity; Coupled hypersensitivity; Statistical investigations

Combined cobalt (Co) and nickel (Ni) allergy is considered to be due to independent sensitization and not to cross-sensitivity (11). This phenomenon has been discussed by several authors (2, 8, 1). In this study 1 310 patients suspected of having allergic contact dermatitis were subjected to patch test procedures in the period 1977–80. In total 211 cases of sensitization to Co, to Ni or to both metal allergens were found (Table I).

Although the interpretation of the rates of positivity by carefully performed epicutaneous tests revealed only a momentary restricted insight into the grade of hypersensitivity, in principle most in vitro tests have the same disadvantage. In this study of 211 individuals with Co and/or Ni allergy the rate of hypersensitivity to each one of the metals was statistically compared. In a selected group (76 cases, including 37 cases of dermatitis of the hands) of the previously described 211 cases, in a combined nickel and cobalt allergy was found, the same statistical study was performed.

## MATERIALS AND METHODS

Patch tests were performed during the inactive phase of dermatitis using commercial (Trolab-Hellerup, Denmark) allergens (NiSO<sub>4</sub> 2.5% and CoCl<sub>2</sub> 1% in petrolatum according to the standardized procedures recommended by the International Contact Dermatitis Research Group (ICDRG) (6). Both metals (Ni and Co) were applied symmetrically on the right and the left side of the back respectively at a reliable distance from each other. Simultaneously the various other antigens of the adapted routine ICDRG standard battery (6) (Table VII) were tested. For patch testing, uniform standard patches (IMECO) (6) were used.

The results were read after 72 hours (24 hours after removal of the patches). The skin reactions were graded extreme (+++), strong (++) , weak (+) or negative, as indicated in the literature (13) (Tables I–VI).

There are many ways of investigating the data statistically with regard to a possible positive association between Co and Ni allergy. One adequate way is by looking at various 2×2 tables formed by aggregation of certain patient categories, carrying out the chi-square test for association in such a table and computing the associated odds ratio.

## RESULTS

A coupled Co and Ni allergy was found in 76 out of the 1 310 cases (5.8%). For solitary cobalt and nic-

Table I. 1310 patients tested for contact dermatitis with Ni and Co

Total excluding Ni- and Co-double negatives, i.e. cell Co<sup>-</sup>, Ni<sup>-</sup> is 211. Double-positives (Ni and Co) were seen in 76 cases

Co	Ni				Total
	+++	++	+	-	
+++	13	3	0	3	19
++	11	4	3	13	31
+	14	13	15	34	76
-	31	25	29	1 089	1 184
Total	69	45	47	1 149	1 310

kel allergy the percentages were respectively 3.8% (50/1 310) and 6.5% (85/1 310) (Table I).

In Table I the various actual rates of reactivity to Co are summarized in connection with concomitant and individual corresponding findings in Ni patch tests in 76 cases with a combined allergy. In this table 85 cases of solitary Ni reactions and 50 cases of solitary Co reactions are also included. The data of a similar comparable investigation in a group of 91 (out of 211 cases) patients with dermatitis of the hands are summarized in Table II.

Considering the first chi-square analysis (Table III) based on all 1 310 positive vs. Ni negative, we have here a highly significant  $\chi^2$  statistic and an odds ratio of about 20: i.e. a Ni-positive patient has 20 times greater odds of being Co-positive than has a Ni-negative patient.

Similarly, from the second 2x2 table (Table IV) we see that in this study an extreme Ni patient has 48 times greater odds of being extreme Co-positive than have other patients (Ni-strong, -weak or -negative).

Similar analyses can be based on the group of patients obtained by excluding all double-negative

Table II. 91 patients with allergic dermatitis of the hands excluding Ni and Co double-negatives

Co	Ni				Total
	+++	++	+	-	
+++	9	2	0	1	12
++	4	0	1	5	10
+	10	6	5	14	35
-	13	9	12	x	34
Total	36	17	18	29	91

Table III. Chi-square tests

Positive vs. negative (all patients from Table I)

Co	Ni		Total
	+++ ++ +	-	
+++	76	50	126
++			
+			
-	85	1 099	1 184
Total	161	1 149	1 310

$\chi^2=298$ , d.f. = 1,  $p < 0.001$ , odds ratio = 20.

cases (Table V) and the group of confirmed dermatitis of the hands patients, again excluding all double-negatives (Table VI). It is that there are no data available concerning the number of patients who have confirmed dermatitis of the hands but are double-negative with respect to Co and Ni. However, by excluding double-negatives the positive association between Co and Ni reactions is weakened: a Co-negative patient has to be Ni-positive, i.e. a negative relation between Co and Ni has been introduced. However, we still see statistical significant associations between Co and Ni extreme positive reactions when double-negatives are excluded.

In Table VII the data are summarized regarding the numbers of positive reactions to other antigens of the standard ICDRG battery (6) in relation to actual levels of positivity in combined nickel and cobalt allergy. Statistical analysis revealed that within our study population with 'combined' positive reactions to Ni and Co (76 cases), a  $p$ -value between 0.05 and 0.10 was found with respect to the

Table IV. Chi-square test

Extreme positive vs. other (all patients from Table I)

Co	Ni		Total
	+++	++ +	
+++	13	6	19
++	56	1 235	1 291
+			
-			

$\chi^2=154$ , d.f. = 1,  $p < 0.0001$ , odds ratio = 48.

Table V. *Chi-square test*

All patients from Table I, excluding Ni and Co double-negatives (total 211 patients). Extreme positive vs. other

Co	Ni		Total
	+++	++ + -	
+++	13	6	19
++	56	136	192
+			
-			
Total	69	142	211

$\chi^2 = 12$ , d.f. = 1,  $p < 0.001$ , odds ratio = 5.

association between the strength of these reactions and positive reactions to these other antigens. There were no significant differences seen in the frequency of positive reactions to other antigens, when the combined Ni and Co reactions were weakly and strongly positive respectively. It could be noted that in our study the general question of a possible association between 'single' positive reactions to Ni or Co and positive reactions to other antigens has not been considered.

## DISCUSSION

Weakly positive (+) epicutaneous tests might be due to an 'increased skin reactivity' as a result of several simultaneous positive tests and can sometimes be negative if single tests are made. This can be avoided by testing the antigen on different occasions with a reliable time interval.

However, following this last procedure there remains uncertainty about the value of the comparisons of 'actual levels' of positive reactions that may be due to variations in individual immune reactivity as a function of time. For this reason both Ni and Co were tested simultaneously.

Several speculations are made in the literature with regard to the development of coupled Co and Ni allergy (2, 7). Important relevant features are: possibly genetic predisposition, the potential sensitizing properties of both metals, the concomitant occurrence of both metals in products and the quantities of release of both metals.

No significant correlation could be found as yet between metal allergy and HLA-antigens (10) in particular and polyvalent allergy and HLA antigens (4) in general. By use of the human maximization

test, Co was found to be a grade 3 sensitizer (3). By use of the guinea pig maximization test, Co was found to be a stronger sensitizer (grade 5) (12) than Ni (grade 3) (5).

In humans, solitary positive patch tests to Co are reported to be relatively rare (9), though most Ni objects usually contain traces of Co (6).

In our study an extreme (+++) solitary Co reaction was seen only in 3 cases, though the same was noted in 13 cases connected with an extreme reaction to Ni (Table I). In a significantly higher incidence (31 cases) an extreme solitary reaction was seen to Ni. From the original group of 1310 patients, only 126 cases (9.6%) showed a positive reaction to Co. In 15 patients, coupled weak, but true, Co reaction (+) was seen.

Of the 91 patients with allergic dermatitis of the hands, only 37 demonstrated a coupled allergy. Solitary reactions to Co and Ni were seen respectively in 20 cases and 34 cases. In this group (Table II) extreme reactions to both metals associated with incidence of dermatitis of the hands were seen in 9 cases. Eight out of these nine patients were female. These findings are consistent with a previous report (7) which indicates that simultaneous sensitization to Co and Ni is rare and that coupled Ni and Co allergy occurs mainly in female patients with dermatitis of the hands.

The statistical conclusion is that in the population of patients examined for possible contact dermatitis, there is a strong association between Ni and Co reactions, extending to the actual level of reaction too: extreme goes with extreme; extreme or strong with extreme or strong; extreme, strong or weak with extreme, strong or weak! The same goes

Table VI. *Chi-square test*

Extreme positive vs. other. Allergic dermatitis of the hands patients from Table II, excluding Ni and Co double-negatives

Co	Ni		Total
	+++	++ + -	
+++	9	2	11
++	14	66	80
+			
-			
Total	23	68	91

$\chi^2 = 21$ , d.f. = 1,  $p < 0.001$ , odds ratio = 21.

Table VII. *Positive reactions to other antigens of the routine ICDRG standard battery in relation to the actual levels of Ni and Co positivity within the population with combined Ni and Co allergy*

a = potassium dichromate 0.5%; b = paraphenylenediamine 2%; c = parabens 15%; d = neomycine sulphate 20%; e = cobalt chloride 1%; f = ethylene-diamine 1%; g = nickel sulphate 2.5%; h = chinosform 5%; i = colophony 20%; j = thiuram-mix 1%; k = wood tars 12%; l = carbamix 3%; m = wool alcohols 30%; n = mercapto-mix 2%; o = epoxy resin 1%; p = PPD-mix 0.6%; q = balsam of Peru 25%; r = naphthyl-mix 1%; s = cinamic aldehyde 2% (all in petrolatum); t = formaldehyde 2% (in aqua)

Levels of positivity of combined Ni/Co allergy	Number of cases	Number of cases of combined Ni/Co allergy in combination with other positive tests	Number of cases of isolated Ni/Co allergy
Ni +, Co +	15	4 (a/q/dm/q/c)	11
Ni +, Co ++	3	2 (t/aln)	1
Ni +, Co +++	0	0	
Ni ++, Co +	13	4 (a/i/l/h/l/m)	9
Ni ++, Co ++	4	2 (ikq/kq/l)	2
Ni ++, Co +++	3	0	3
Ni +++, Co +	14	6 (a/a/i/b/l/j/l/n)	8
Ni +++, Co ++	11	0	11
Ni +++, Co +++	13	3 (m/t/l)	10
Total	76	21	55

for the smaller population of patients with confirmed allergic dermatitis of the hands (Table VI).

Of course such an association does not need to be present in the population of interest, e.g. the 'whole Dutch population' and thus there could be a strong association in the type of people who came to the out-patient clinic and who were examined in this study. In 76 cases of combined nickel and cobalt allergy, 21 positive reactions to other antigens of the standard ICDRG battery were seen. With respect to these data the important question arises, whether (Table VII) within the population of combined Ni and Co allergy the levels of positivity (weak or strong) to these metals might be related to reactions against other antigens tested concomitantly. In cases of strong (+++) combined Ni and Co allergy, 3 out of 13 cases (Table VII) showed positive reactions to other antigens: carbamix +++ (one case), formaldehyde +++ (one case) and wool alcohols ++ (one case). When both Ni and Co were found to be both weakly positive (+), 4 out of 15 cases showed positive reactions to other antigens: parabens + (one case), neomycine ++, wool alcohols +, balsam of Peru + (one case), chromium +++ (one case) and balsam of Peru ++ (one case).

From the statistical analysis ( $p$ -value between 0.05 and 0.10) it might be concluded that it is unlikely that within the population of combined Ni and Co allergy 'increased skin reactivity' due to positive reactions to other antigens tested had a significant influence on the data reported in our study.

Individual immunological predisposition and circumstantial release of different quantities of metal allergens responsible for sensitization and clinical allergy remain important factors for the interpretation. However, it can be concluded from the material examined in this study that extreme positive patch test reactions to Co are rare and 'extreme' Ni patients have about 50 times greater odds of being 'extreme' Co positive.

Based on these clinical data it is tempting to assume that on the cellular level (Langerhans' cells and/or macrophages and/or T-lymphocytes) a high grade of sensitivity to Ni might trigger facilitation of clinical Co allergy.

#### ACKNOWLEDGEMENT

We are grateful to Dr R. D. Gill (Dept. of Mathematical Statistics, Mathematical Centre, Amsterdam) for his contribution in the statistical analysis.

#### REFERENCES

1. Cronin, E.: Metals (chapter 7). Contact Dermatitis, p. 279. Churchill Livingstone, Edinburgh, London, New York, 1980.
2. Fregert, S. & Rorsman, H.: Allergy to chromium, nickel and cobalt. Acta Dermatovener (Stockholm) 46: 144, 1966.
3. Kligman, A. M.: The identification of contact allergens by human essays. III. The maximisation test: a procedure for screening and rating contact sensitizers. J Invest Dermatol 47: 393, 1966.

4. Lidén, S., Beckman, B., Cedergren, B., Groth, O., Göransen, K. & Wählby, L.: Lack of association between allergic contact dermatitis and HLA antigen of the A and B series. *Acta Dermatovener (Stockholm)* 61: 155, 1980.
5. Magnusson, B. & Kligman, A. M.: The identification of contact allergens by animal assay. The guinea pig maximisation test. *J. Invest Dermatol* 52: 268, 1969.
6. Malten, K. E., Nater, J. P. & van Ketel, W. G.: Patch Testing Guidelines. Dekker en van de Vegt, Nijmegen, 1976.
7. Menne, T.: Relationship between cobalt and nickel sensitization in female. *Contact Dermatitis* 6: 337, 1980.
8. Müller, R. & Breucker, G.: Kobalt als arbeitsbedingtes Ekzematogen und als Koppelungsallergen mit Chrom und Nickel. *Dermatol Wochenschr (Leipzig)* 154: 277, 1968.
9. Rystedt, I.: Evaluation and relevance of isolated test reaction to cobalt. *Contact Dermatitis* 5: 223, 1979.
10. Silvennoinen-Kassinen, S., Honen, I., Tülikainen, A. & Karvonen J.: No significant association between HLA and nickel contact sensitivity. *Tissue Antigens* 14: 459, 1979.
11. Van den Berg, J. J. & Epstein, W. L.: Experimental nickel contact sensitization in man. *J Invest Dermatol* 44: 413, 1963.
12. Wahlberg, J. E. & Boman, A.: Sensitization and testing of guinea pigs with cobalt chloride. *Contact Dermatitis* 4: 128, 1978.
13. Wilkinson, D. S., Fregert, S., Magnusson, B. et al.: Terminology of contact dermatitis. *Acta Dermatovener (Stockholm)* 50: 287, 1970.

## Transient Lymphomatoid Papulosis in Mycosis fungoides

A. Aronsson, N. Jonsson and E. Tegner

Departments of Dermatology and Pathology,  
University of Lund, Lund, Sweden

Received March 4, 1982

**Abstract.** During PUVA treatment a 66-year-old woman with mycosis fungoides in stage III suddenly developed widespread papulonodular lesions of alarming clinical and histological appearance. There was rapid spontaneous and complete regression of the eruptions, which was probably an expression of transient lymphomatoid papulosis in connection with MF.

**Key words:** Mycosis fungoides; Lymphomatoid papulosis; PUVA treatment

Photochemotherapy with psoralens and ultraviolet-A (PUVA) generally has a beneficial effect

on mycosis fungoides (MF) in the plaque stage (5). However, a few cases of internal dissemination during successful external treatment have been described (4, 8). Spreading of skin tumours during PUVA treatment of MF in both plaque and tumour stages has also been observed (10). We report a woman with MF who during a short series of PUVA treatments developed acute, papulonodular lesions with a malignant clinical and histological picture.

### CASE REPORT

The patient was a 66-year-old woman who had had widespread, slowly progressing skin lesions for about 30 years, and who had experienced accentuated itching for the last few years. She complained of gradually increasing discomfort, with discoloration, dryness, and irritation of the skin, and was admitted to the Department of Dermatology. On admission she had no constitutional symptoms. The skin showed poikiloderma with reticulate hyperpigmentation. Brownish plaques with scaling were present, especially on the trunk and legs, some with prominent infiltration and a tendency to tumour formation. Freely mobile lymph nodes were palpated in axillae and groins. Treatment with potent topical corticosteroids gave good symptomatic relief, and some regression of both skin lesions and lymph nodes occurred. After three treatment sessions with PUVA (total 1.5 J/cm<sup>2</sup>) multiple symmetrical purplish papulonodules suddenly developed, mostly on the trunk, but some also on the extremities (Fig. 1).

During the ensuing week fulminating lesions continued to appear. The patient remained in good general condition. 10 days after the appearance of the initial lesions, spontaneous regression occurred. The papules became haemorrhagic, crusted, and fell off. Some lesions literally melted down, and some were infected with *Staph. aureus*. This process lasted for one week, after which the skin was completely free from lesions.

Histopathological examination of an infiltrated plaque showed a parakeratotic stratum corneum with clusters of leukocytes. Subepidermally there was a dense infiltrate of lymphoid cells with some atypical cells, and small collections of atypical cells were found in the lower and middle epidermis. The findings were consistent with MF. Histopathological examination of a fresh violaceous papule (Fig. 2) showed ulceration with dense infiltration in the dermis by irregular polymorphic cells having hyperchromatic nuclei, sometimes with a prominent nucleolus. The findings indicated malignant lymphoma, probably immunoblastic sarcoma. Another punch biopsy was taken from a resolving lesion: lymphocytic vasculitis was predominant, with numerous erythrocytes in the dermis. Infiltrates of irregular lymphoid cells were still present around the vessels, although the changes were now less

**Note:** The patient is included in the current investigation by the Scandinavian Mycosis Fungoides Study Group.