

NICKEL AND COBALT DERMATITIS

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IT IS a matter of common knowledge that nickel is a potent eczematous sensitizer in industry as well as in the more casual nonindustrial contacts. There have been many reports of dermatoses which attest to this. Cobalt is a less ubiquitously used metal than nickel, and consequently, it would not appear to be so important from the medical point of view, but for reasons that will be presented, we feel it is probably as important as nickel. It is the purpose of this paper to describe briefly some of the sources for encountering nickel and cobalt, to present a case of eczematous sensitivity to these metals, and to discuss certain theoretical aspects concerning eczematous sensitizations which this case illustrates.

SOURCE AND USES OF NICKEL AND COBALT

These are best shown by the tables, which make no pretense at being exhaustive or complete; however, it is believed they cover the principal situations. Table I lists the major possibilities for industrial contact with nickel.

TABLE I. INDUSTRIAL CONTACTS WITH NICKEL

	Mining and refining ore
	Nickel plating
	Many alloys
.	Industries using these alloys
	Contaminant of cobalt

Table II lists the chief alloys containing nickel or cobalt and their qualitative compositions. Table III gives articles utilizing nickel-containing alloys, and Table IV lists the most common sources for encountering cobalt.

NONSPECIFIC FACTORS AFFECTING THE DEVELOPMENT OF A SENSITIZATION TO NICKEL OR COBALT

These factors are especially important in industry, but they also play a role in casual nonindustrial contacts. In industry, one of the most important factors influencing the development of a sensitization to either of these metals is irritation arising from any source. The irritation as a rule is from two causes: (a) concomitant substances such as solvents used for degreasing objects to be plated, or (b) cleansers the workmen use on themselves. Either of these, by causing some degree of inflammation in the skin, apparently favors the development of a sensitization. Such an observation has experimental verification. Landsteiner and Di Somma¹ found that in guinea pigs the sensitizing effect of picric acid was definitely enhanced by applying the material to previously inflamed skin. Environmental factors also influence the development of a derma-

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titis. Bulmer and Mackenzie² in a study of "nickel rash" came to the following conclusions:

"1. An insufficient cooling power in the worker's environment is the most important single factor in the causation of nickel rash.

"2. An increased skin temperature allied with an alkaline sweat increases the irritability of the exposed parts, lowers their resistance, and increases their susceptibility to irritation."

TABLE II. ALLOYS CONTAINING NICKEL OR COBALT

NAME	QUALITATIVE COMPOSITION*
Allegheny metal, Enduro metal	Ni Fe C Cr
Alnico	Ni Co Al
Chromel	Ni Cr
Coin alloys	Ni Cu
Constantan	Ni Cu
Duralium	Cr Co Ni Mo Be
German silver	Ni Zn Cu
Hastelloy	Ni Cu Al Mo
Illium	Ni Cr Mo Cu Fe
Invar	Ni Fe C
Manganin	Ni Cu Mn
Monel metal	Ni Cu Fe Mn
Nichrome	Ni Fe Cr Mn
Nobilium	Cr Co Ni Mo Be
Permalloy	Ni Fe Co
Platenite	Ni Fe C
Stainless steel	Varying compositions—Fe Cr Ni Mn Si C (Allegheny metal is one)
Stellite	Co Cr W C
Ticonium	Cr Co Ni Mo Be
Vitalium	Cr Co Ni Mo Be

*The qualitative composition should be interpreted as giving a possible make-up for the alloy in question rather than the exact composition, in as much as in some instances certain of the ingredients are optional.

TABLE III. ARTICLES UTILIZING NICKEL-CONTAINING ALLOYS

Chemical apparatus
Cutlery
Coins
Decorative purposes on automobiles and buildings
Electrical resistances in common household articles
various physical apparatus
Electrical equipment
Hardware
Heating units in household appliances
Jewelry
Kitchen equipment
sinks
table tops
cabinets
Medical and dental alloys
Meter and yard scales
Pendulum rods
Propeller and turbine blades
Sheet metal work
Sporting goods
Stainless steel objects
Surveyor's tape
Wire gauze and screens

Schwartz and associates,³ in a study of dermatitis arising in a factory manufacturing cemented carbides, believed that a dusty atmosphere containing cobalt particles favored the development of a sensitization to the cobalt.

TABLE IV. POSSIBLE SOURCES FOR ENCOUNTERING COBALT

INDUSTRIAL	NONINDUSTRIAL
Mining and refining ore	Cutting tools
Making of cobalt alloys	Pigments
Stellite alloys	Tattoo pigments
Tungsten carbide industry	Adhesive of fly paper
Carbology	Alloys used in medicine and dentistry
Glass industry	Duralium
Ceramic industry	Nobilium
Enamels	Ticonium
Pigments	Vitallium
Contaminant of nickel*	Vitamin B ₁₂
Electrical industry	Contaminant of nickel*

*It is important to realize that all commercial nickel contains some amount of cobalt as a contaminant. Because of their close chemical similarity it is not possible to separate them completely at a cost compatible with the ordinary commercial uses of nickel.

CASE REPORT

W. B., a 23-year-old white man, had noticed for many years that at the site of contact with metal he would develop a dermatitis. As it had never been particularly severe, he had not sought medical attention. However, he shortly contemplated marriage, and as he intended wearing a wedding band, he wondered whether he would develop a dermatitis at the site of the band. For this reason he came in for advice. At the time he was first seen he presented a papulovesicular eruption around the left wrist which corresponded to the location of his wrist watch strap. In view of the history that he reacted to almost any metal, he was tested with a wide variety of metals in order to determine the range of his sensitivities. Table V lists the materials with which the patient was first tested.

TABLE V. DIAGNOSTIC PATCH TESTING

MATERIAL	RESULT
Chromic nitrate	0
Chromic chloride	0
Potassium dichromate	0
Cobaltous nitrate	+++
Copper (cupric) acetate	0
Ferric chloride	0
Ferric nitrate	0
Ferrous sulfate	
Ferric sulfate	0
Gold (auric) chloride	+
Manganous chloride	0
Potassium permanganate	0
Nickelous nitrate	+++
Platinic chloride	0
Silver nitrate	0
Zinc nitrate	0

All chemicals applied as a 2 per cent aqueous solution. All readings at 48 hours.

As is seen from Table V, the patient gave a strong positive patch test reaction to cobalt and to nickel and a weaker one to gold. In order to determine the degree of sensitivity, tests were made with dilutions of nickel and cobalt. On patch testing he reacted to cobaltous nitrate in concentrations as low as 1 part in 10,000. In the case of nickel he did not react to concentrations below 1:200.

Intradermal testing was done, and Table VI gives the results of these tests.

TABLE VI. INTRADERMAL TESTS

SUBSTANCE	FORMULA	CONCENTRATION	REACTION
Cobaltous nitrate	$\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	1:10,000	++
Cobaltous nitrate	$\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	1:100,000	+
Nickelous nitrate	$\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	1:10,000	+
Nickelous nitrate	$\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	1:100,000	±
Vitamin B ₁₂ (Cobione)		1:100,000	+

A volume of 0.02 to 0.03 ml. injected for each test. All tests read at 48 hours. Normal controls tested with above were negative.

It is interesting to note that the patient gave a delayed tuberculin type reaction to vitamin B₁₂ (Cobione*) which is known to be a cobalt-containing compound. Apparently this is the first report of a sensitivity to the crystalline vitamin B₁₂.†



Fig. 1.—Reaction the patient experienced from wearing a jacket having metal clasps. The patient is lying on his back and the involved areas are on the superior aspect of the right shoulder.

Further evidence of the sensitivity of the patient is furnished by Fig. 1, which shows the reactions the patient experienced from contact with metal clasps. The patient worked as a pharmacist and wore a jacket which was fastened over the shoulder with three metal clasps. At the site of contact with each clasp a papulovesicular dermatitis developed. These clasps were investigated and found to contain nickel.

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†Recently, Young, Ulrich and Fouts⁴ reported a patient who reacted to a vitamin B₁₂ concentrate, but the patient did not react to the crystalline vitamin.

THEORETICAL CONSIDERATIONS

One of the problems in eczematous sensitizations that has both theoretical and practical interest is the exact nature of the sensitizing allergen. There is reason to believe that the simple chemical itself does not cause the development of the sensitivity, but that a combination of the simple chemical with some bodily constituent (presumably protein) is the complete antigen (Landsteiner and Jacobs⁵ and Gell⁶). Assuming this to be true, and were the nickel combined in vitro in such a fashion that it could not unite with protein, then when this synthesized nickel compound was put into a sensitized host (assuming the combination formed in vitro to be stable) there would not be a reaction. To test this hypothesis, two compounds, namely hexammine nickel (II) bromide and tri-ethylenediamine nickel (II) bromide were synthesized and their ability to elicit patch test reactions in the patient compared with nickelous nitrate. The results are shown in Table VII. It is important to realize that all of these compounds were tested at identical molarity, which means that the equal volumes of the solution employed provided equal numbers of combined nickel atoms. If a difference in reaction was then obtained with the test solutions this could only be ascribed to the fact that the amount of nickel available to the body as nickel ions varied in the different compounds. In view of the fact that all 3 were in solution, the difference in availability could only be attributed to the degree to which these compounds dissociated. For the purposes of this discussion, the dissociation of nickelous nitrate can be considered as complete or 100 per cent; that of hexammine-nickel (II) bromide can be considered as roughly one-half that of the nickelous nitrate, whereas the dissociation of tri-ethylenediamine nickel (II) bromide can be considered as zero when compared to the other two. Our patch test results paralleled the extent of the dissociation, which would be evidence for the fact that nickel, in order to elicit a reaction in the sensitized host, has to be able to combine with the tissues.*

TABLE VII. COMPARATIVE PATCH TESTS WITH NICKEL COMPOUNDS

SUBSTANCE	FORMULA	REACTION
Nickelous nitrate	$\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	+
Hexammine nickel (II) bromide	$\text{Ni}(\text{NH}_3)_6\text{Br}_2$	±
Tri-ethylenediamine nickel (II) bromide	$\text{Ni}(\text{NH}_2\text{C}_2\text{H}_4\text{NH}_2)_3\text{Br}_2$	0

All tested at 0.02 M strength. All readings at 48 hours.

It is believed that in eczematous sensitizations where the complete antigen is formed in vivo it at least in part leaves the site of its formation by way of the lymphatics (Rostenberg^{7, 8}). Our patient afforded us an interesting visual corroboration of this. Fig. 2 shows a lymphangitic reaction which occurred at the site of an intradermal injection of one of the cobalt solutions. The illustration shows a lymphangitic streak extending up toward the axilla. This reaction appeared approximately 24 to 48 hours after the injection. One naturally thinks of the possibility of an infection with such an occurrence, but

*Similar experiments were done with cobalt salts, but the results were not satisfactory. We believe the failure in the case of cobalt can, however, be explained on grounds that do not alter the argument but that would not be profitable to discuss at this point.

the solution had previously been checked for sterility and was again checked after the reaction was noted and was found to be sterile. The same solution was used on several others without any reaction being noted. It is, of course, possible that at the moment of making the injection a few organisms were introduced. There is no way to disprove this possibility. This type of lymphangitic reaction has been described by Haxthausen⁹ and one of the substances which yielded such a reaction was nickel.



Fig. 2.—Lymphangitic streak extending toward axilla after an intradermal test to cobalt. Photograph is of volar aspect of right arm.

It is interesting both from the practical and theoretical points of view that nickel and cobalt are relatively cross reactive. Table VIII gives the results reported in the literature of simultaneous testing with the 2 elements.

The cross sensitivity of nickel and cobalt is not, we believe, sufficiently well appreciated and has, of course, obvious practical importance. It indicates that

TABLE VIII. RESULTS OF TESTING WITH NICKEL AND COBALT IN THE SAME PATIENT

AUTHOR	NUMBER OF CASES	SENSITIVE TO BOTH	SENSITIVE TO NICKEL ALONE	SENSITIVE TO COBALT ALONE
Cormia and Stewart ¹⁰	4	3	1	0
Goldman ¹¹	2	0	2	0
Haxthausen ¹²	12	7	4	1
Rabeau and Ukrainczyk ¹³	4	0	4	0
Rostenberg and Perkins	1	1	0	0
Stewart ¹⁴	1	1	0	0
Total	24	12	11	1

a person who is intensely sensitive to the one element is most likely sensitive to the other and, indeed, if he is not sensitive at the time of testing will almost certainly develop a sensitivity to the other. This means that when a metal or an alloy is to be substituted for either nickel or cobalt the substituent should be free from both. The importance of this is well brought out in the report by Deissler and Sheets,¹⁵ whose patient developed a dermatitis from a metallic denture. On testing she was found to be sensitive to nickel, and accordingly a denture was made from a nickel-free alloy but the patient reacted just as violently as before. On further investigation it was found that she was also cobalt sensitive, and that the new alloy contained cobalt. Had the facts just related been known, the cobalt-containing alloy would never have been employed.

On the theoretical side it at first glance seems odd that there should be a cross reaction between two different elements, for in immunologic reactions in general, and eczematous sensitizations in particular, one ordinarily has a high degree of specificity. For example, in the case of persons sensitized to 2:4 dinitrochlorobenzene the body distinguishes the positional isomers of dinitrochlorobenzene and reacts most strongly to those bearing the closest resemblance to the original sensitizing isomer (Rostenberg and Kanof¹⁶). As was pointed out in that article, it would appear that for a person to react to a simple chemical other than the one to which he was sensitized, the new compound must be able to form conjugates which have a geometric (stereochemical) resemblance to the sensitizing compound. Now when the types of functional groups of proteins with which cobalt and nickel are likely to react are considered, it is seen that on the basis of present chemical knowledge it is not possible to assert that there would be a difference. For instance, both cobalt and nickel form coordination compounds with amine groups, sulfhydryl groups, hydroxy groups, oxime groups, and β diketones, among others. The stability of the linkages is greater when two functional groups are on the same molecule so that ring formation, including the metal atom in the ring, can take place. There is only one significant difference from a chemical point of view in the types of compounds formed by these two elements. As trivalent cobalt forms much more stable coordination compounds than divalent cobalt, the compounds formed in the skin would presumably have cobalt in a trivalent form for oxygen from the air is

sufficient to oxidize divalent cobalt to trivalent cobalt in the presence of coordinating reagents; whereas, nickel would stay in the divalent condition. Furthermore, the trivalent cobalt always forms 6 such linkages, whereas nickel usually forms only 4 linkages.

When the geometrical configuration of these compounds is considered in light of present knowledge it is again not possible to assert that there would be a significant difference. All that can be said with confidence is that in considering the possible linkages formed between these metal atoms and materials in the skin, the difference between the radii of the links with cobalt or with nickel are quite small, of the order of $0.05\text{\AA}$.

So it is seen that in the case of both nickel and cobalt, conjugates (linkages) with similar spatial configurations would be formed and it is thus reasonable that they should cross react.

A more difficult problem to answer is why compounds of several other elements such as chromium, copper, and platinum do not also cross react, since these elements show quite similar reactivities toward the functional groups just mentioned. That these last mentioned elements do not yield cross reactions in an individual eczematously sensitive to nickel and to cobalt would seem to indicate that there are serious defects in the knowledge of the chemical properties of these elements and perhaps that the chemistry of these substances with living tissues is not the same as in the test tube.

Finally, it has been mentioned that this patient was also sensitive to gold. The problem arises: was his gold reaction another example of a cross reaction or was it an independent sensitization? It is believed that it was of the latter nature for several reasons: (1) Quantitatively the intensity of the sensitivity to gold was much less than to either cobalt or nickel. (2) This combination is apparently a unique one, that is, the literature, as has been mentioned, gives many examples of cross reactivity between nickel and cobalt, but none between gold and either of these. It would therefore appear as if the development of sensitivity to gold in this case was a fortuitous event and not immunologically related to the other sensitizations. (3) If the sensitization to gold stemmed from the cobalt-nickel sensitization there is no chemical reason known why the patient should not also have been sensitive to several other metals, especially platinum, and he was not. It is realized that none of these reasons decisively answers the question as to the nature of the sensitization to gold but it is felt that the weight of the evidence preponderantly favors the view that it was an independent unrelated sensitization. Until more chemical knowledge is available no final answer can be given.

SUMMARY AND CONCLUSIONS

1. Sources for encountering nickel and cobalt are listed.
2. The role of nonspecific factors, such as agents conducive to cutaneous inflammation, humidity, and dust, in the genesis of eczematous sensitizations is discussed.
3. A case of a man extremely sensitive to nickel and to cobalt and less so to gold is described.

4. This is the first report of a man who gave a delayed tuberculin type reaction to crystalline vitamin B₁₂ (Cobione).

5. It was shown that in order to get a reaction nickel had to be in an available form, presumably so that it could unite with the tissue proteins.

6. An example of a lymphangitic reaction to an intradermal test with a simple chemical is given.

7. The cross reactivity of nickel and cobalt was considered and the importance of this from the practical side was pointed out. On the theoretical side possible reasons for the cross reactivity were advanced and the many defects in our knowledge were emphasized.

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