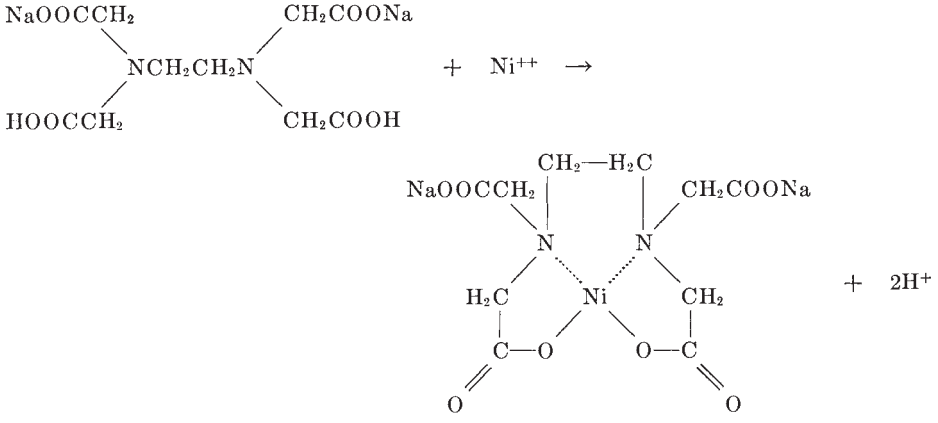
PRELIMINARY AND SHORT REPORT

CHELATION DEACTIVATION OF NICKEL ION IN ALLERGIC ECZEMATOUS SENSITIVITY

ABNER KURTIN, M.D. AND NORMAN ORENTREICH, M.D.

The chelating agents are a group of compounds with unique properties. They have the ability to form soluble, non-ionizing stable complexes (chelates) with elements of the alkaline earth and heavy metal series. Cations which have been so complexed can no longer be precipitated out of solution by their usual precipitating agents. They become part of a soluble complex anion, and are bound so securely that they no longer exhibit any characteristic cationic properties. They have not been removed physically from solution, but have been deionized and chemically deactivated. The chelating principle usually depends upon the natural tendency to ring formation by compounds containing five or six atoms with coordinate valence.

The following formulas explain the chelation reaction of disodium ethylenediamine tetraacetic acid (ETDA)* with ionic nickel:



The chelating principle was first recognized by Werner (1) in 1901. Morgan and Drew (2) coined the name chelation in 1920 after the Greek work for claw (chele). As far as we can ascertain it was first used biologically (3) in a study of the effect of free calcium ion concentration on the contraction of the ventricle of the frog heart. The anticoagulant action of a chelate (calcium withdrawal) was investigated by Dyckerhoff, Marx and Ludwig (4) in 1942. Kissin and Natelson (5) reported their application for urinary calculi in 1950. A chelate was first used on the skin by Popovici, Geschickter and Rubin (6) in a study of systemic absorption and its effect on blood calcium levels. Others (7, 8) have suggested that chemical interference between the allergen and the skin might have therapeutic and preventive application in allergic contact eczematous dermatitis. Rostenberg and Perkins (9) demonstrated that a bound metallic ion can no longer cause allergic reaction.

The chelation phenomenon suggested an application for the inhibition of metal cutaneous allergic sensitivity reactions. As an experimental approach to this consideration, 10 proven

Received for publication February 23, 1954.

* The chelating agent used in this work was disodium ethylenadiaminetetraacetic acid which was contributed by Dr. Albert Hemming of Geigy Pharmaceuticals as Sequestrene Na_2.

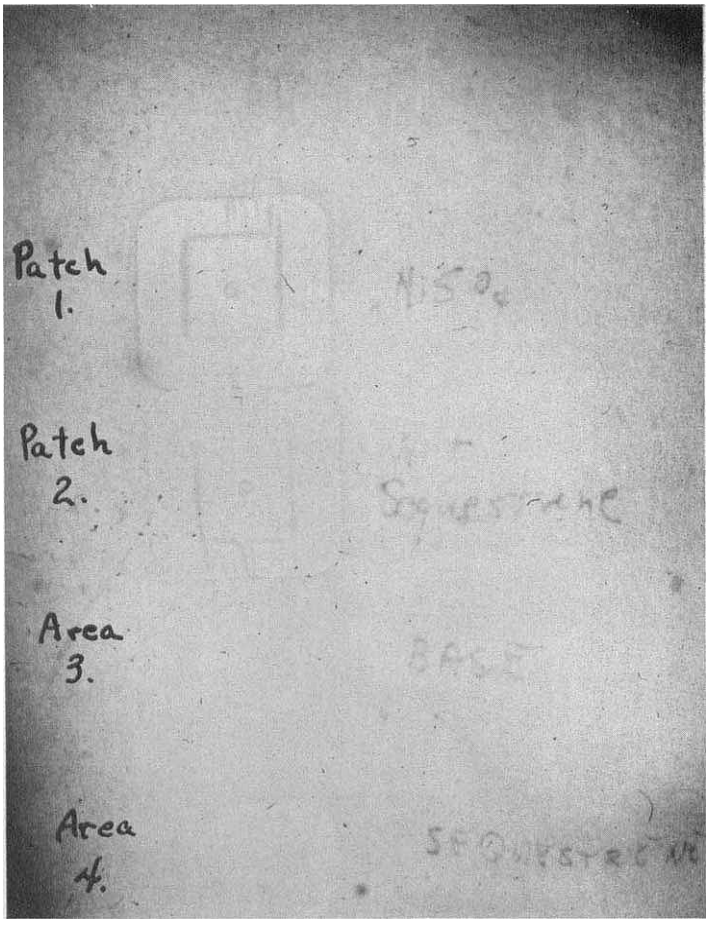


FIG. 1. This photo demonstrates testing method. Patch test 1—2% $NiSO_4$. Patch test 2—2% $NiSO_4$ completely chelated with 10% ETDA. Area 3—control base over which a patch test with 5% $NiSO_4$ was applied. Area 4—the ETDA protective ointment over which a 5% $NiSO_4$ patch test was applied.

cases with strong nickel allergic sensitivity by patch test were used. These subjects were simultaneously tested with a completely chelated identical concentration of nickel.** It was shown that such complete chelation totally prevented the allergic contact sensitivity reaction even though the nickel was still in solution. We have called this phenomenon "chelation blockade".

To test the preventive efficacy of an ointment containing a chelate, the following was done to a nickel sensitive subject: 2 patch tests of 5% nickel sulfate were applied over uniform layers of the chelating ointment and its control base. The inhibitory action of the chelating ointment contrasted to the base is well shown in the photograph.

** Complete chelation of a solution containing ionized nickel can be tested by adding dimethyl glyoxine and demonstrating the failure to develop the typical strawberry-red precipitate (the acid nickel salt of dimethyl glyoxine which would form with uncomplexed nickel). In this work 2% $NiSO_4$ was chelated with 10% ETDA.

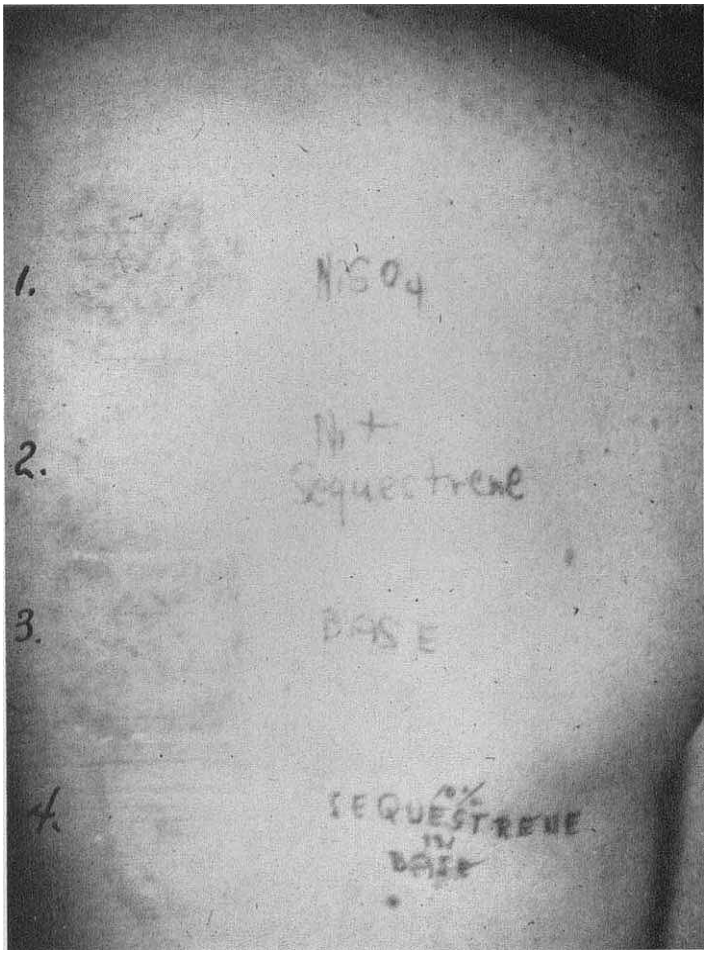


FIG. 2. 48 hours reading demonstrates the following: Test 1—3 plus allergic eczematous contact reaction. Test 2—Negative. Test 3—3 plus allergic eczematous contact reaction. Test 4—Plus-minus allergic reaction which disappeared in 24 hours. (There is a moderate amount of adhesive type reaction in this case.)

A parallel experiment to the one above was done in a hair dye-sensitive patient and no chelation deactivation was noted. We believe that this experiment indicates that a chelate is not a general cutaneous allergic inhibitor.

DISCUSSION

These findings possibly open a new and practical approach to the therapeutic and prophylactic management of the common metal sensitivities. The usual presence of trace metals in toiletries, therapeutic agents and household products may be a cause for the continuation of a dermatitis in highly sensitive patients. The addition of chelating compounds to these and other commonly handled materials may eliminate this factor.

There are other possible applications of "chelation blockade" as a research tool. Those under study are listed:

1) Protective and therapeutic medication.

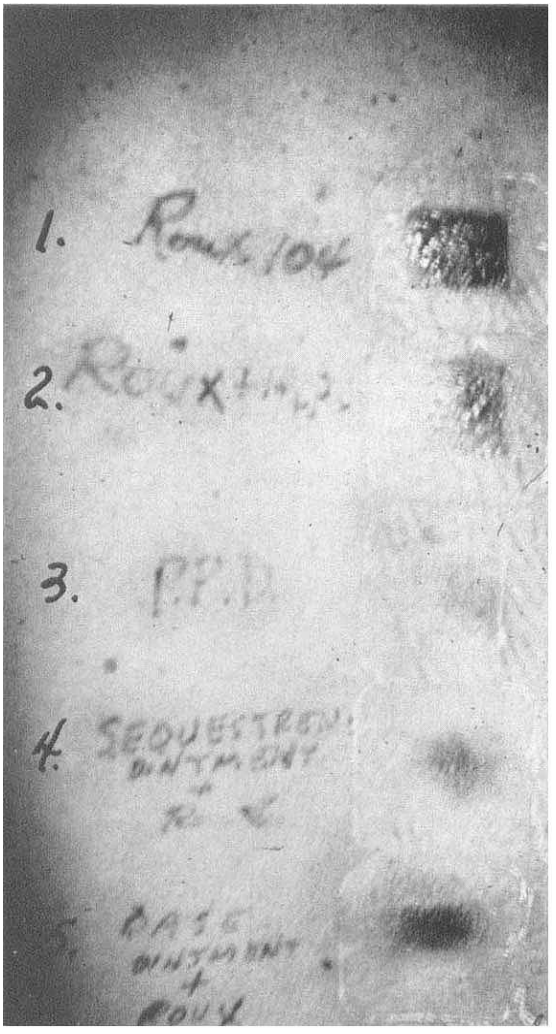


FIG. 3. 48 hours reading demonstrates the following: Patch test 1—Roux 104 (4 plus). Patch test 2—Roux 104 plus hydrogen peroxide (4 plus). Patch test 3—Paraphenylene diamine (3 plus). Patch test 4—Roux 104 over ETDA ointment (3 plus). Patch test 5—Roux 104 over control base (3 plus).

2) The inhibition of metal catalysts in cutaneous enzyme reactions (e.g. copper in melanogenesis, etc.).

3) Elucidation of patch testing with complex materials to eliminate the role of a possible heavy metal component as a factor in the reactions elicited.

4) Deprivation of essential trace metals to pathogenic organisms.

5) Treatment of calcifying diseases of the skin (osteoma cutis, scleroderma, etc.).

6) Removal of heavy metal deposits in the skin (beryllium, silver, mercury, etc.).

CONCLUSIONS

1) Chelation of nickel ion in solution will deactivate its antigenic ability to produce allergic eczematous reactions of sensitivity in nickel patch test positive cases.

2) An active chelating agent applied in ointment form will inhibit the appearance of a positive nickel patch test applied over the ointment site.

3) A chelating agent is not a general cutaneous allergic inhibitor.

REFERENCES

1. WERNER, A.: Veber acetylaceton verbindungen des platius. Berichte Deutsche Chemische Gesellschoft. **34:** 2584–2593, 1901.
2. MORGAN AND DREW: Researches on Residual Affinity and Coordination—Pt 2. Acetylacetones of Selenium and Tellurium. J. Chem. Soc. **117:** 1456–1465, 1920.
3. HASTINGS, MCLEAN, EICHELBERGER, HALL AND DA COSTA: The ionization of calcium magnesium and strontium citrates. J. Biol. Chem. **107:** 351–376, 1934.
4. DYCKERHOFF, H., MARX, R. AND LUDWIG, B.: Uber den wirkungsmechanismus und die verwandbarkeit eineger blutgerinnungshemmender organischer substranzen. f.d. Ges. Exper. Med. **110:** 412–422, 1942.
5. KISSIN, B. AND NATELSON, S.: Chelating agents and urinary calculi. Science, **112:** 367, 1950.
6. POPOVICI, A., GESCHICKTER, C. F. AND RUBIN, M.: Experimental control of serum calcium levels in vivo. Proc. Soc. Exp. Biol. & Med. **74:** 415, 1950.
7. ANDERSON, N. P.: Neutralization as a therapeutic principle in contact dermatitis. Arch. Dermat. & Syph. **49:** 176–182, 1944.
8. GOLDMAN, L.: Prevention of irritation and sensitization of skin to chemical compounds. South. M. J. **37:** 290–301, 1944.
9. ROSTENBERG, A. JR. AND PERKINS, A. J.: Nickel and cobalt dermatitis. J. Allergy, **22:** 466–474, 1951.