9-44

Reactions in Green Tattoos.

The Significance of the Valence State of Chromium

L. J. A. LOEWENTHAL, M.D., M.R.C.P., D.T.M. & H., Johannesburg, Union of South Africa

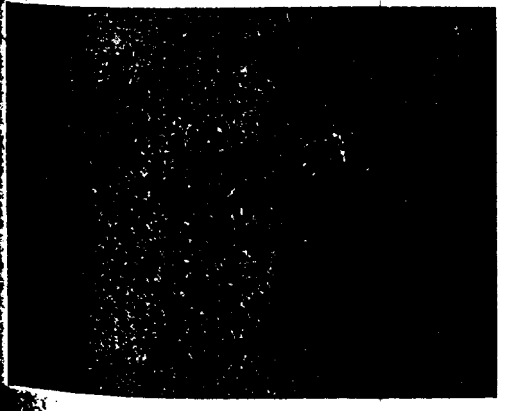
Allergic reactions in green tattoos have now been reported in seven cases,[1-5] of whom four showed a foreign-body and/or sarcoid reaction on histologic examination. The typical case acquires an allergic sensitivity to dichromates and later presents a reaction in areas tattooed with chrotne green many years before. The fact that the chrome in dichromates and the chrome used in tattooing differ fundamentally in their chemical, biologic, and allergenic behavior has hitherto been ignored. In the absence of cross sensitivity between chrome in its different states of valence another explanation of this phenomenon must be sought.

Report of a Case

The patient, a white man, age 35, was first seen in August, 1958. Employed as a bricklayer, he was in frequent contact with wet cement. For one year he has had a persistent eczema of the hands and legs, with occasional generalized dissemination. Patch tests with potassium dichromate were positive and a diagnosis of cement dermatitis was made. His employment was changed but no improvement of his skin condition took place. He was next seen a year later, in August. 1939, with the eczematous dermatitis unchanged; he stated that the green areas of a tattoo of the arm, made over 20 years ago, had become raised and slightly irritable about 6 months previously, and this was confirmed on examination (Fig. 1). First one and later the other five green areas were excised for chemical and histologic examination and further tests made (Table). This excision, without any alteration in treatmerit, was followed by rapid improvement in his eczematous dermatitis. With the exception of one slight flare-up within 3 weeks of the excision his skin has remained clear for a period of 10 weeks *to* date.

Submitted for publication Oct. 30, 1959.
From the South African Institute for Medical Research, Johannesburg.

Fig. 1.—Swollen green portions of tattoo. Healing biopsy wound on right.



Cutaneous Tests.—In August, 1958, patch tests to potassium dichromate, in dilutions of 0.1% to 2%. were strongly positive. A patch test with moistened Portland cement was negative.* In August, 1959, these tests were repeated, with the same results. Chromic acid (CrO_3) also gave a positive result in a dilution of 0.1%. The following patch-tests were negative: chroniiuni sulfate, 0.4% and 0.2%; chromic chloride, 0.5%. The same solutions were pricked into the skin of the volar surface of the forearms; examination at frequent intervals during tho following four weeks showed no reaction of the type which would be classed as positive in intradermal testing with. e.g., tuberculin.

Histology.—The six affected green areas were excised. One was used for chemical investigation without previous fixation; two others were fixed in 10% formalin, embedded in paraffin wax, and cut at various Icvels.

Foreign Matter: Unstained sections showed numerous foreign particles, the majority of them being green; others, where presumably a portion of blue tattoo had been included in the excised tissue, were black and ainorphous and resembled in every rcspcct the deposits of carbon seen in blue tattoos. Both specimens revealed a few light-blue to violet particles, of an almost constant diameter of 20μ and of circular or oval outline.

* A series of over 20 cases of cement dermatitis has shown similar results, i.e. a positive reaction to 0.1% potassium dichromate and/or chromic acid solution, and a negative reaction to various types of cement (unpublished data).

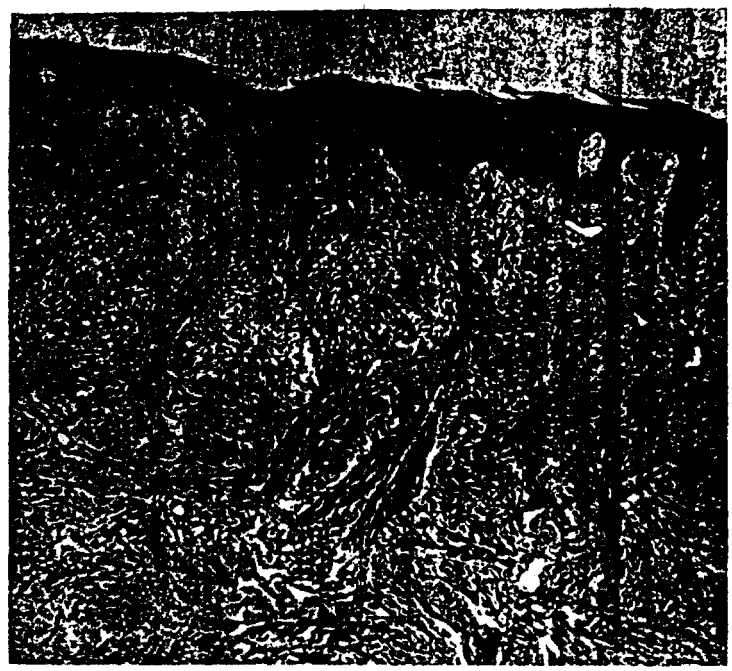


Fig. 2.—Sarcoid type of reaction in upper cutis (first specimen). Hematoxylin and eosin stain, × 38.

These particles did not show refraction under polarized light. The green particles varied in size from that of coarse melanin granules as seen in chromatophores to 30μ or more. Many of the larger ones showed a definite crystalline structure, but it was not possible to determine a typical shape: however all of them refracted polarized light from one or more facets. In addition there was much "dust" consisting of particles so small that their color could not be determined.

Tissue Changes: These were localized to areas where foreign particles were found, and it was obvious from the examination of stained sections that these areas were all situated in the upper half of the corium. The two specimens showed certain differences, in that the one contained granulomas of sarcoid type (Fig. 2), while the other showed a predominantly lymphocytic and giant-cell infiltrate (Fig. 3); both contained numerous giant cells of the foreign-body type in whose cytoplasm many of the foreign particles were seen. In areas where only carbon particles were present, these were lying free between collagen bundles as is normally found in uncomplicated tattoos, or at the most were surrounded by a moderate lymphocytic infiltrate. But where the carbon occupied the same area as green and blue particles the foreign-body granuloma included them all, and the giant cells did not seem to discriminate between the various substances; thus

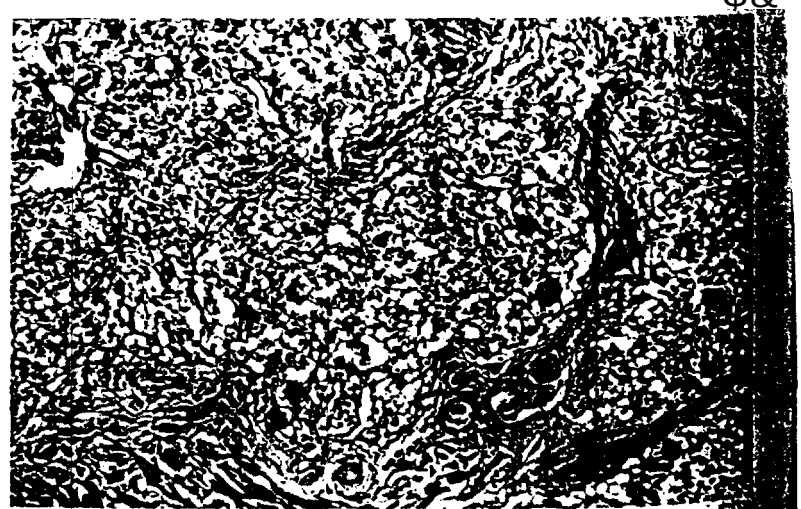


Fig. 3.—Foreign body type of reaction (2d specimen). Hematoxylin and eosin; reduced 30% from mag. × 150.

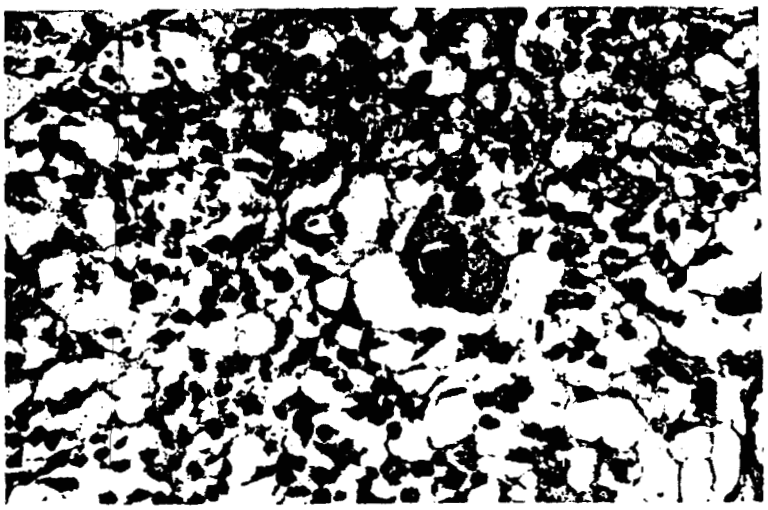


Fig. 4.—Giant cell containing green, blue, and black particles. Hematoxylin and eosin; reduced 30% from mag. × 600.

a single giant cell was seen containing one blue and several green and black particles (Fig. 4). There was little evidence of fibrous tissue reaction round the clearly outlined granulomas of both specimens; fibroblasts and mast cells were scanty. In one specimen the overlying epidermis showed early eczematous changes in the form of lymphocytic spongiosis (Fig. 5).

Chemical Analysis.—One of the excised pieces was tested for the presence of chrome. The specimen (0.5 gm.) was dried, ashed in platinum, and the ash dissolved in 2 ml. of 2 N sulphuric acid. The solution gave a strong positive spot test for chromium using *sym.*-diphenylcarbazide. The color was compared with that from a standard chromate solution and corresponded roughly to a 1/100,000 concentration; this indicated an approximate Cr concentration in the wet specimen of 40 ppm; the test is sensitive down to a 1/625,000 concentration. A specimen of skin from a non-tattooed man gave no spot test for chromium when treated in exactly the same way.

Comment

Dermal Reactions to Foreign Substances.

Shelley and Hurley [6] give a comprehensive list of foreign substances which may provoke granuloma formation in man, but chrome is not included. It is, however, mentioned in a subsequent publication.[7] Although their careful studies conclusively proved the allergic origin of zirconium-deodorant granulomas, the allergic nature of certain granulomatous tattoo reactions has been recognized since the publication of the first example by Paul Unna Jr.[8] in 1930 (not P. G. Unna, as sometimes misquoted). Furthermore the allergic origin of beryllium granulomas was clearly demonstrated by Sneddon,[9] who produced sarcoid-like granulomas after an interval of three weeks at

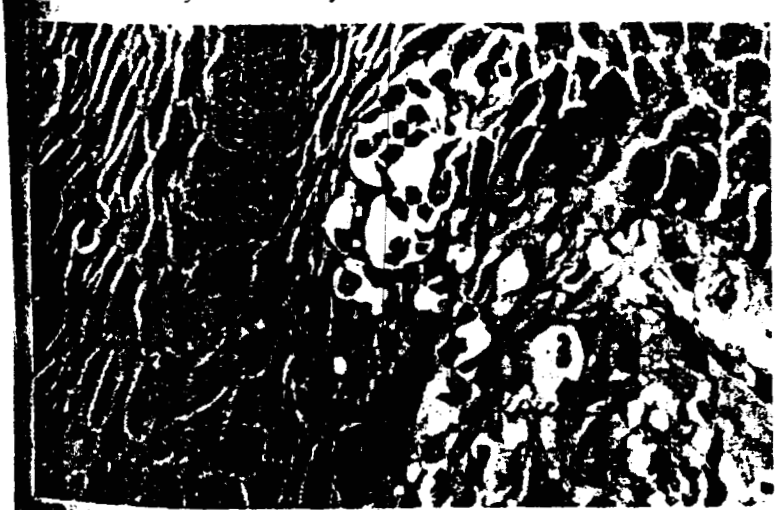


Fig. 5.—Focus of basal lymphocytic spongiosis overlying chrome granuloma. Hematoxylin and eosin; reduced 27% from mag. × 600.

the site of positive (eczematous) patch-test reactions to beryllium sulfate and nitrate.

A full account of tattoo reactions up to 1954 was given by Beerman and Lane,[10] and further examples of allergic granulomatous reactions to the cinnabar of red tattoos are given by Sulzberger and Tolmach,[11] who also mention some of the rare examples of analogous reactions in green tattoos,[2,4] which they assume *to* represent an allergic hypersensitivity to chrome salts.

The case presented here, like those of Björnberg,[5] demonstrates how chrome particles may lie quiescent in the skin for up to 20 years and then provoke a granulomatous reaction when a proved allergic sensitivity to chrome develops. An interesting theoretical point is the combined presence of dermal and epidermal allergic hypersensitivity *to the same substance,* as seen in many cases of cinnabar tattooing, in berylliosis[9] and, for instance, in concomitant reactions to intradermally injected and epicutaneously applied tuberculin.

The fact that this patient's eczematous dermatitis, which had persisted for two years, recovered promptly after removal of the intradermally situated chrome is relevant here, as is the finding of eczematous foci overlying a granulomatous lesion (Fig. 5). The question of the coexistence of allegedly immunologically distinct epidermal and dermal sensitivities, including those provoked by chromates, is well presented by Epstein,[12] and in the discussion which appears after his paper.

The simultaneous Occurrence of two distinct types of granuloma (sarcoid-like, Figure 2, and nonsarcoid foreign-body type, Figure 3) in neighboring lesions from the same patient and through the same allergic mechanism is also noteworthy. No explanation is advanced for this phenomenon; it may, however, account for the fact that either type of granuloma may be seen around silica particles.

Chemical Considerations.—The occurrence of simultaneous or subsequent reactions to chrome compounds by epidermal and intradermal application would hardly warrant such extensive treatment were it not for a fact that has been overlooked previously: *chromium in the form of bichromates and chromium compounds os used* by *the ta'too "artist"* ore *chemically and biologically different substances,* and no cross sensitivity between them has been demonstrated.

Chromium exists in various oxidation states, so that it is capable of forming different compounds according to its state of valence. In accordance with the recommendations of the International Union of Chemistry, bivalent chrome may he referred to as Chromium (II). tervalent chrome as Chromium (III) and sexivalent chrome as Chromium (VI).

Sexivalent chronic forms chromates and dichromates (bichromates) whose ions have a double negative charge and are therefore anions. Chromates and dichromates are strong oxidizing agents, the chromium (VI) being easily reduced to Chromium (III) in acid solution, as occurs in the two-bath chrome tanning process.[12] The great majority oi cases of allergic sensitivity to chrome are proved to be sensitive to dichromates, whether these are encountered in cement, Javel water, fur-dyeing, photography or any other of the numerous processes in which these salts are used.

Chromium (III) aiid its salts form cations. Strong oxidizing agents are required to transforni these to chromate or dichromate ion.[14] Only two of the tervalent chrome compounds are relevant to this discussion.

Chromium (III) sulfate is used in tanning leather, either directly, as in most modern tanneries in the United States, or indirectly, by reduction of sexivalent sodium dichromate.

Chromium (111) oxide is a powder often called *chrome green* or *Casalis green.* It and its closely related pigment, *Guignet's green,* are the principal green dyes used by the tattoo "artist."[2] Chrome green is a very stable substance, resistant to acids and insoluble in water, alcohol, and acetone; conversion to sexivalent chromic oxide requires

a powerful oxidizer, such as ozone.[15] Guignet's green, which is a mixture of hydrous Chromium (111) oxides, may contain blue-gray particles of small size, containing large amounts of water. This is a possible explanation of the bluish-violet particles seen in the histologic preparations described previously.

Chrome green is prepared by reduction of an alkali dichromate with sulfur, carbon, ammonium chloride, or organic materials.[16] The usual method is by heating sodium dichromate with sulfur, and leaching out the sodium sulfate with water. This should theoretically remove all traces of dichromate, in view of its high solubility. This question will be referred to later. Guignet's green is prepared from potassium dichromate and boric acid; it will thus be seen that Chromium (VI) compounds fonn the starting point in the preparation, of both pigments.

Biological Differences.—Herrmann and Speck[17] were forced to account for the interactiori of (sexivalent) chromate with nucleic acids in tissues by postulating that it is first reduced to Chromium (111) compounds, "as is evidenced by the greenish colour of the residue." Visek, Whitney, Kuhn, and Comar,[18] using radioactive chrome, investigated its metabolism in animals; they found that cationic tervalent chrome was bound by plasma proteins, while anionic sexivalent chrome entered the erythrocytes as previously shown by Gray and Sterling,[19] where it was bound by globin. Metjer[20] cites other examples of contrasting biological behavior, such as differing solubility at body pH and the role of tervalent chrome in activating the succinic dehydrogenase-cytochrome system, originally described by Horecker, Stotz, and Hogness.[21] The interaction of chrome and collagen provides another example, as tervalent chrome is believed to form aggregates which chelate with amino and carboxyl groups of the protein (Gustavson,[22] Bowers and Kenton,[23]) while no combination between sexivalent chrome and protein was demonstrable by paper electrophoresis (Magnus[13]).

Allergenic Differences.—Walsh[24] states unequivocally that "trivalent and metallic chromium apparently are not irritating or sensitizing substances." There is, however, one solitary report of sensitivity to tervalent chrome: Morris[25] patch-tested a case of shoe-leather dcrniatitis with 0.2% basic Chromium (I1I) sulfate and obtained a positive result. He mentions similar, unpublished, results in other cascs. He emphasizes that tervalent chromium sulfate is not related to the sexivalent chromates and dichromates which dermatologists use for patch-testing in suspected dermatitis from shoes, with largely negative results, but he did not state whether standard patch-tests with dichromates were done in his own cases; this omission is a serious one in view of Walsh's remarks in the next paragraph. Certainly Bett[26] has recently reported thnt, of 27 patients shown to be leather-sensitive, only 5 were dichromate-positive, arid concludes that the association of dichromate and leather sensitivities is a weak one. Tests with tervalent chrome were not done.

Apart from Morris[25] no writer has demonstrated or even seriously considered the possibility of sensitization by tervalent chrotne. Walsh[24] endeavored to explain hypersensitivity to sexivalent chroniates in some cases of shoe-leather dermatitis as follows: "Theoretically, when tanning is completed, all this chromium is in trivalent form. . . . Since apparently trivalent chromium is never sensitizing, the frequent coexistence of dermatitis from shoe leather and hypersensitivity to chromate is difficult to explain. . . . There may be small amounts of residual chromate that was not reduced during the 'two bath' tanning process. Some of the trivalent chromium may be oxidized to chromate during some subsequent processing of leather."

More specifically, the same problem of antigenic dissimilarity arises in tattooed patients who have shown allergic reactions around deposits of tervalent chrome after being sensitized to sexivalent dichromates. The Table presents such data as have been collected to date. In reading this Table two

Reactions in Green Tattoos: Summary of Tests Employed

Case	Author	Nature of Test	Substance	Valence	Result
1	Björnstad[1]	Patch	Dichromate	VI	+*
2	Rostenberg et al.[3]	None			—
3	Heilesen[4]	Patch	Stand. chrome (presum dichromate)	VI	+
		Patch	Chromium-containing paint	?	+
4	Bonnell & Russell[5]	Patch	"Chrome" (variety not stated)		Neg.
5	Björnberg[6]	Patch	Dichromate 0.5%	VI	1st test neg., later +
		Patch	Chrome green (commerc.)	III	Neg.
6	Björnberg	Patch	Dichromate 0.5 %	VI	+
		Patch	Chrome green	III	Neg.
7	Björnberg	Patch	Dichromate 0.5 %	VI	+
		Patch	Chrome green	III	Neg.
8	Loewenthal	Patch	Dichromate, 2%, 0.5%, 0.1%	VI	All +
		Patch	Chromium sulfate 0.4% & 0.2%	III	Both Neg
		Patch	Chromic chloride 0.5%	III	Neg.
		Prick	Chromium sulfate 0.2%	III	Neg.
		Prick	Chromic chloride 0.5%	III	Neg.

* The patient presented only eczematous eruptions on the green tattooed areas.

facts must be remembered: (1) that a patch test with "chrome-containing paint" gives little evidence of the valence state of the chromium present, for reasons to be given later, and (2) that patch tests with chrome green are unlikely to be informative, in view of the insolubility of this substance.

Similar results were obtained by Jaeger and Pelloni[27] in their investigation of cement dermatitis; cases who showed a marked epicutaneous sensitivity to dichromates were negative to patch tests with tervalent and metallic chrome. This assumed incapability of tervalent chrome to act as a sensitizer is reflected in Hilt's[28] claim to have prevented sensitivity to Chromium (VI) by its in situ reduction to Chromium III.

All in all, then, a sensitivity to tervalent chrome need not be considered in the problem of reactions to green tattoos. We must therefore postulate that sesivalent chrome is either formed or liberated at the surface of the particles of chrome green in the tattoo.

A. *Oxidation* of *Tervalent Chrome Green to Sexivalent Dichromates.*—The insolubility of chrome green, as well as the necessity for a powerful oxidizer,[15] make it unlikely that a change in valence by raising the oxidation number from 3 to 6 could take place as a result of the oxidation-reduction reactions present in living tissues.

B. *Presence of Sexivalent Chrome as an Impurity in Chrome Green.*—The presence of visible admixtures in the form of bluish-violet particles in the histologic preparations argues against the chemical purity of the chrome green used by the tattoo "artist." Although the leaching used in the normal preparation of Chromium (III) oxide from dichromate and sulfur should theoretically remove all traces of dichromate, it is probable that hurried or careless preparation could result in contamination. Thus Walsh[24] writes that ". . . the pigments used in paints, inks, rubber, and ceramics, namely lead and barium chromate and trivalent chromium oxide, are very insoluble and seldom if ever cause dermatitis. These substances may sometimes contain traces of a soluble hexavalent chromate that will cause difficulty in the evaluation of patch tests." The situation with regard to chrome pigments is therefore precisely that which was outlined in the case of chrome-tanned leather.

Summary and Conclusions

A further case of reaction in a green tattoo is presented.

Sarcoid and nonsarcoid types of foreign-body granuloma occurred in adjacent clinically identical lesions. The association of dermal granulomatous and epidermal eczematous allergic reactions is noted.

The previous tacit acceptance of simultaneous allergic sensitivity to dichromates and chrome green is rejected; no antigenic similarity exists between tervalent and sexivalent chrome and cross sensitivity does not occur. A possible explanation is given for this apparent paradox.

Dr. G. H. Findlay (Section of Dermatology, University of Pretoria) and Dr. D. A. Sutton (Pneumoconiosis Research Laboratories, Johannesburg) offered valuable suggestions in discussing this case; the latter performed the chemical examination of tissue. The photomicrographs are by M. Ulrich of the South African Institute for Medical Research.

604, Medical Centre, 209, Jeppe St.

REFERENCES

1. Björnstad, R.: Idiosyncratic Eczema with Eruptions Also in Old Tattooing (Case Presentation), Acta dermat.-venereol. 30:379, 1950.

2. Rostenberg, A.; Brown, R. A., and Caro, M. R.: Discussion of Tattoo Reactions with Report of a Case Showing a Reaction to a Green Color, Arch. Dermat. & Syph. 62:540-547, 1950.

3. Heilesen, B.: Chromium Allergy as the Probable Cause of Eczema in Tattooing (Case Presentation), Acta dermat.-venereol. 33:255, 1953.

4. Bonnell, J. A., and Russell, B.: Skin Reactions at Site of Green and Red Tattoo Marks (Case Presentation), Proc. Roy. Soc. Med. 49: 39:23-29, 1959.

5. Björnberg, A.: Allergic Reactions to Chrome in Green Tattoo Markings, Acta dermat.-venereol. 39:23-29, 1959.

6. Shelley, W. B., and Hurley, H. J.: The Allergic Origin of Zirconium Deodorant Granulomas, Brit. J. Dermat. 70:75-101, 1958.

7. Shelley, W. B.; Hurley, H. J.; Mayock, R. L.; Close, H. P., and Cathcart, R. T.: Intradermal Tests with Metals and Other Inorganic Elements in Sarcoidosis and Anthraco-Silicosis, J. Invest. Dermat. 31:301-303, 1958.

8. Unna, P., Jr.: Quecksilberüberempfindlichkeit und Tätowierung, Arch. Dermat. u. Syph. 160: 153-155, 1930.

9. Sneddon, I. B.: Berylliosis: A Case Report, Brit. M.J. 1:1448-1450 (June 18) 1955.

10. Berman, H., and Lane, R. A. G.: "Tattoo": Survey of Some Literature Concerning Medical Complications of Tattooing, Am. J.M. Sc. 227:444-465, 1954.

11. Sulzberger, M. B., and Tolmach. J. A.: Allergische Aufflammungsreaktionen in roten Tätowierungen, Hautarzt 10:110-114, 1959.

12. Epstein, S.: Contact Dermatitis Due to Nickel and Chromate. A.M.A. Arch. Dermat. 73: 236-255, 1956.

13. Magnus I. A.: The Conjugation of Nickel, Cobalt, Hexavalent Chromium and Eosin with Protein as Shown by Paper Electrophoresis, Acta dermat.-venereol. 38:20-31, 1958.

14. Pauling L.: College Chemistry, San Francisco, W. H. Freeman and Co. Ed. 2, 1957, p. 589.

15. Udy, M. C.: The Physical and Chemical Properties of Chromium, in Chromium, Vol. I, Chemistry of Chromium and Its Compounds, M. J. Udy, Editor, New York, Reinhold Publishing Corp., 1956, p. 118.

16. Chalupski, V. H.: The Manufacture and Properties of Chromium Pigments, Ibid pp. 357-384.

17. Herrmann, H., and Speck, L. B.: Interaction of Chromate with Nucleic Acids in Tissues, Science 119:221, 1954.

18. Visek, W. J.; Whitney, I. B.; Kuhn, U. S. G., III and Comar, C. L.: Metabolism of Cr^{51} by Animals as Influenced by Chemical State, Proc. Soc. Exper. Biol. & Med. 84:610-615, 1953.

19. Gray, S. J., and Sterling, K.: Tagging of Red Cells and Plasma Proteins with Radioactive Chromium, J. Clin. Invest. 29:1604-1613, 1950.

20. Baetjer, A. M.: Relation of Chromium to Health, in Chromium, Vol. I, Chemistry of Chromium and Its Compounds, M. J. Udy, Editor, New York, Reinhold Publishing Corp., 1956, pp. 76-109.

21. Horecker, B. L.; Stotz, E., and Hogness, T. R.: The Promoting Effect of Aluminum, Chromium and the Rare Earths in the Succinic Dehydrogenase-Cytochrome System, J. Biol. Chem. 128:251-256, 1939.

22. Gustavson, K. H.: Some Protein-Chemical Aspects of Tanning Processes, Adv. in Protein Chem. 5:353-421, 1949.

23. Bowes, J. H., and Kenton, R. H.: The Effect of Deamination and Esterification on the Reactivity of Collagen, Biochem J. 44:142-152, 1949.

24. Walsh, E. N.: Chromate Hazards in Industry: Council on Industrial Health, J.A.M.A. 153: 1305-1308, 1953.

25. Morris, G. E.: Cross-Sensitization of the Feet and Hands Due to Chrome-Tanned Leather Shoes and Gloves, New England J. Med. 257: 567, 1957.

26. Bett, D. C. G.: The Potassium Dichromate Patch Test, Transactions of St. John's Hospital Dermatological Society No. 40:40-48, 1958.

27. Jaeger, H., and Pelloni, E.: Tests épicutanés aux bichromates, positifs dans l'eczéma au ciment, Dermatologica 100:207-216, 1950. Cited by Hilt.[28]

28. Hilt, G. La Dermite du chrome hexavalent dans le cadre des dermites eczémateuses par sensibilisation aux métaux, Dermatologica 109:143-174, 1954.