Chelation Therapy in Nickel Poisoning

F. WILLIAM SUNDERMAN SR., M.D., PH.D.
Hahnemann Medical College and Hospital,
Philadelphia, PA 19102

ABSTRACT

For the treatment of acute poisoning from the inhalation of nickel carbonyl, sodium diethyldithiocarbamate (Dithiocarb) has proved to be a specific antidote; tetraethylthiuram (Antabuse) is effective to a lesser degree; d-penicillamine and dimercaprol (BAL) have limited therapeutic value.

For the treatment of nickel eczema and dermatitis, favorable response has been obtained by placing patients on a diet of low nickel content together with the oral administration of Dithiocarb or Antabuse.

No specific therapy has been advanced for the treatment of nickel cancer in humans. In experimental animals, Dithiocarb has an inhibitory effect on the production of rat rhabdomyosarcomas induced by the intramuscular implantation of nickel subsulfide, and N-methyl formamide inhibits the growth of transplantable nickel fibromas in rats. It is suggested that for the treatment of tumors arising from the implantations of nickel-containing prostheses in humans, chelation therapy be considered.

It is only within recent decades that the hazards of exposure to nickel and nickel compounds have come to be recognized. In an interesting review of “On the Uses of Nickel Sulphate in Medicine,” Kolipinski in 1911 stated, “Nickel and nickel salts, excepting for the very poisonous nickel carbonyl, have no place or record in toxicology.” He dismissed the case of Emperor of Austria, Franz Josef, where an illness was attributed to nickel poisoning, as being doubtful. Kolipinski elaborated on the exceptional medicinal value of nickel salts for the treatment of epilepsy, chorea, migraine, and neuralgia. He also noted that “nickel acts as a sedative and tonic of peculiar and elective power in controlling the damaging effects of sexual vice on the nervous system.”

And now, since World War II, the uses of nickel for medicinal purposes have been completely abandoned, and it has become recognized that in addition to nickel carbonyl, exposure to nickel and other nickel compounds may be deleterious to health.

On the other hand, nickel is probably an essential trace element for mammalian life. In 1936, Bertrand and Nakamura suggested that nickel may play a normal physiological role in metabolism. In 1974, Schwartz indicated that nickel is probably an essential element for the life and health of animals.

Before considerations of current therapy for nickel poisoning, it may be informative to indicate the relative...
TABLE I
Toxicity of Nickel and Its Compounds

<table>
<thead>
<tr>
<th>Nickel (Colloidal and Powdered)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Dogs</td>
<td>LD = 10 to 20 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Acute oral Dogs</td>
<td>Tolerated: 1 to 3 g/kg</td>
<td></td>
</tr>
<tr>
<td>Nickel Salts (Cl, NO2, SO4, O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous Dogs</td>
<td>LD = 10 to 20 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous Rabbits</td>
<td>LD = 1.3 g/kg</td>
<td></td>
</tr>
<tr>
<td>Acute oral Rats</td>
<td>LD50 = 2.0 g/kg</td>
<td></td>
</tr>
<tr>
<td>Chronic oral Cats</td>
<td>Tolerated: 25 mg/kg/day for 200 days</td>
<td></td>
</tr>
<tr>
<td>Skin application Human</td>
<td>1:10,000 evokes sensitivity reaction</td>
<td></td>
</tr>
</tbody>
</table>

Nickel Carbonyl - Ni(CO)4

<table>
<thead>
<tr>
<th>Inhalation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicie</td>
<td>LC50 = 0.067 mg/liter for 30 minutes</td>
<td></td>
</tr>
<tr>
<td>Inhalation Rats</td>
<td>LC50 = 0.24 mg/liter for 30 minutes</td>
<td></td>
</tr>
<tr>
<td>Inhalation Cats</td>
<td>LC50 = 1.9 mg/liter for 30 minutes</td>
<td></td>
</tr>
<tr>
<td>Intravenous Rats</td>
<td>LD50 = 22 ± 1.1 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous Rats</td>
<td>LD50 = 21 ± 4.2 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal Rats</td>
<td>LD50 = 15 ± 1.4 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

It will be seen that solutions of colloidal nickel or nickel salts have a high degree of toxicity when given either intravenously or subcutaneously. On the other hand, the ingestion of nickel or nickel salts has a relatively low degree of toxicity. When given orally, it will be seen that dogs are able to tolerate doses of metallic nickel and nickel compounds as high as three grams per kilogram of body weight. It should also be mentioned that in previous years, it had been believed that the ingestion of milligram quantities of nickel contained in food and also derived from food cooked in stainless steel utensils was without detectable deleterious effects on the health of people. However, it now appears that in persons hypersensitive to nickel, even minute quantities may be deleterious.

The most toxic of all the compounds of nickel that are encountered in industrial operations is nickel carbonyl (Ni(CO)4). The LD50 values for a 30 minute exposure to Ni(CO)4 for mice and rats are 0.067 and 0.24 milligram per liter, corresponding to 10 and 33 parts per million, respectively.

TABLE II
Types of Nickel Poisoning

Inhalation (Ni(CO)4, Ni, Ni3S2, NiO, Ni3O3)

Acute
- Pneumonitis with adrenal cortical insufficiency; hyaline membrane formation; pulmonary edema and hemorrhage; hepatic degeneration; brain and renal congestion

Chronic
- Cancer of respiratory tract; pulmonary eosinophilia (Loeffler's syndrome); asthma

Skin Contact
- Primary irritant dermatitis; allergic dermatitis; eczema

Parenteral (Prosthetic Implantations)
- Allergic reactions; osteomyelitis; osteonecrosis; malignant tumors

Oral
- Food and beverage; drugs

Routes of Exposure to Nickel

Any considerations of treatment of nickel poisoning require a knowledge of the physical and chemical characteristics of the nickel compound to which the subject has been exposed, the concentration, length and type of exposure as well as the sensitivity of the host, idiosyncrasy, and presence of disease. The physiologic responses depend in large measure upon the route by which these compounds enter the body and are distributed in the tissues. A wide variety of distribution occurs and nonhomogeneity of distribution appears to be the rule rather than the exception. The routes to which nickel may enter the body are given in table II.

Inhalation

That nickel carbonyl is highly toxic by inhalation is well known from both clinical experience and studies on experimental animals. To a lesser known degree, the inhalation of finely divided nickel, nickel oxides and certain nickel-sulfur containing compounds are also toxic, although the symptoms may not be as well defined as those of nickel carbonyl. The symptoms which follow acute exposure to the vapors...
of nickel carbonyl are of two types,—

initial and delayed. The initial symptoms
are generally mild and disappear quickly
when the subject is brought into uncon­
taminated air. In some cases, the patient
may feel well for as long as several days
after the initial symptoms disappear and
before the onset of the more serious de­
layed reactions. In other cases, the two
stages may merge. In any event, the slow­
ness of the development of symptoms is
such that the victim will usually be aware
of exposure only after the inhalation of a
dosage sufficient to cause serious delayed
effects.17

The most significant pathologic
changes in acute poisoning from the inha­
lation of nickel carbonyl are found in the
lungs. The lungs show a severe degree of
congestion, pulmonary edema, hemor­
rhage, and interstitial pneumonia with
hyaline membrane formation.18,28,38,41 Con­
comitant hepatic and adrenal cortical de­
generation and brain and renal congestion
are also usually observed.

In addition to the acute effects, chronic
exposure to the vapors of nickel carbonyl
and nickel dusts are attended by a high
incidence of carcinoma of the respira­
tory passages as well as pulmonary
eosinophilia (Loeffler’s syndrome)2,45 and
asthma.23

Skin Contact

The most commonly observed toxic
reactions to nickel and nickel compounds
are nickel dermatitis and skin hypersensi­
tivity. The increasing prevalence of nickel
dermatitis and skin sensitivity has been
emphasized by many investigators. It has
been estimated that five percent of all
cases of eczema are caused by contact
with nickel or nickel compounds.30 Ap­
proximately two-thirds of patients with
nickel dermatitis are female. This pre­
ponderance is believed to be related to
the greater exposure to nickel by females.
Nickel dermatitis arises from direct con­
tact of the skin with nickel-containing de­
tergents,21 by working in stainless steel
American-style kitchens,22 from costume
jewelry, garter buckles, watches, metal
straps, spectacle frames, pins, hair clips,
scissors and coins.10,21,22,30,49 Although
most of the investigators have directed at­
tention to the dermatologic manifesta­
tions of nickel sensitivity, nevertheless, it
is noteworthy that other allergic
phenomena may also be encountered.2,45

Parenterally Induced Toxicity

The most frequent toxic reactions of
nickel via the parenteral route result from
surgical use of nickel alloys as implant
materials, such as total hip replacement or
nailing and fixation of fractures. Nickel
sensitized patients with implanted
prostheses containing nickel may develop
loosening of the prostheses, osteo­
myelitis, osteonecrosis, hemangoendo­
thelioma, and malignant tumors.6,24,27,32
The carcinogenic effect of nickel im­
planted in bone has been demonstrated in
rats in which sarcomas developed after
the injection of powdered nickel into the
femurs.13,14 Thus, it seems probable that
the reported malignancies in humans
have been caused by the metal implants.

Ingestion of Nickel

As previously mentioned, nickel in­
gested from foods is believed to be rela­
tively non-toxic.8 The ordinary adult diet,
according to Kent and McCance,4,16
supplies 0.3 to 0.5 milligram of nickel
daily. It may be noted that acidic foods
extract nickel from cooking and storage
utensils and processing equipment.20 The
extent and the amount of nickel extracted
from this source has not been adequately
studied.

Nickel present in drinking water is not
regarded as a health hazard. On the basis
of analyses of nickel concentrations of 969
water supplies in the United States during
1969–1970,28 the average concentration of
nickel in water samples taken at the consumer's tap was 4.8 micrograms per liter. With an estimated daily intake of two liters of water, an adult would consume approximately 10 micrograms of nickel per day in drinking water.\(^2\)

**Antidotal Activity of Chelating Agents in Nickel Carbonyl Poisoning**

For a number of years, our laboratory has studied the hazards of acute and chronic exposure to nickel carbonyl. When we first undertook to treat patients acutely exposed to nickel carbonyl, the only available chelating drugs were BAL (Dimercaprol), d-penicillamine, and EDTA (calcium disodium ethylenediaminotetraacetic acid). Our studies on experimental animals showed that (1) administration of d-penicillamine\(^{18,50}\) had doubtful antidotal effectiveness and produced severe toxic side reactions; (2) EDTA provided no antidotal effects\(^4\); and (3) BAL was only partially effective.\(^1\) With BAL, the LD\(_{50}\) value in rats exposed to nickel carbonyl was found to be increased by a factor of approximately two.\(^3\)

Recognition of the nickel binding and biologic properties of the dithiocarbamates as well as their low toxicity prompted us to initiate studies to determine their possible chemotherapeutic properties as an antidote to acute nickel carbonyl poisoning.

The therapeutic effectiveness of 13 alkyl dithiocarbamates was studied in experimental animals receiving lethal inhalations of nickel carbonyl.\(^5\) A list of the dithiocarbamate compounds that proved to be effective is given in Table III. Of the three dithiocarbamate derivatives that gave complete protection in experimental animals in a dosage of 50 milligrams per kilogram of body weight, sodium diethyl-dithiocarbamate (Dithiocarb) was the least toxic,—the LD\(_{50}\) dosage in mice being 1,500 milligrams per kilogram. It is our opinion that the undesirable side effects and the large dosage required to give complete protection precluded the use of penicillamine in humans. Attention is directed to the partial protection afforded by tetraethylthiuram disulfide (Antabuse), since this drug is readily available and, unlike Dithiocarb, is no longer categorized as an investigational new drug.

The dramatic effectiveness of Dithiocarb in counteracting the lethal effects of nickel carbonyl in experimental animals led us to use this chemical in humans who were accidentally exposed to nickel carbonyl. These exposures occurred in conjunction with a variety of applications of nickel carbonyl in several types of industry. To date, more than 350 workmen exposed to nickel carbonyl have received Dithiocarb. To our knowledge, no exposed workman died who received Dithiocarb within the first five days after exposure. The efficacy of Dithiocarb as a specific antidote for acute nickel poisoning has been reported previously by us.\(^3\),\(^3\),\(^3\)

Oskarsson and Tjälve\(^3\) have recently studied the effects of Dithiocarb and penicillamine on the tissue distribution of \(^{65}\)NiCl\(_2\) in mice. They indicated that nickel diethyldithiocarbamate is lipophilic, whereas nickel-DL-penicillamine complex is hydrophilic and that these differences in chemical properties may determine the

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**TABLE III**

<table>
<thead>
<tr>
<th>Dithiocarbamate</th>
<th>I.P.</th>
<th>Parenteral</th>
<th>Percent Protection Against Ni(CO)(_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LD(_{50})</td>
<td>Dosage</td>
<td></td>
</tr>
<tr>
<td>Na diethyl</td>
<td>1500</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Na dimethyl</td>
<td>&lt;1000</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Na dimethylpropy</td>
<td>&gt;1000</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Na morpholine-l</td>
<td>1000</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Na,N(_2)-ethylene-bis</td>
<td>&gt;500</td>
<td>250</td>
<td>50</td>
</tr>
<tr>
<td>Na 2-(2-oxo-1-imidazol-1-yl)ethyl</td>
<td>&lt;1500</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Na,N(_2)-dimethyl-N,N(_2)-ethylene-bis</td>
<td>&gt;1500</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Tetraethylthiuram disulfide (Antabuse)</td>
<td>&gt;500</td>
<td>250</td>
<td>70</td>
</tr>
<tr>
<td>S,3-dimethylcysteine (Penicillamine)</td>
<td>250</td>
<td>100</td>
<td>(250 fatal)</td>
</tr>
</tbody>
</table>

\(^{\text{Ni(CO)\(_4\) concentration = 0.09 mg per L.}}\)
effects that the chelating agents have on the fate of nickel in the tissues.

A detailed procedure for the administration of Dithiocarb in persons known or suspected of having been exposed to hazardous concentrations of nickel carbonyl have been published. In table IV is given a synopsis of this procedure. In addition to the administration of Dithiocarb, our group and others have found that maintenance of adequate oxygenation and the administration of Cortisol to be valuable adjuncts to therapy.

Nickel Cancer

Excepting for isolated reports, no specific type of chemotherapy has been advanced for the treatment of nickel cancer in man. For example, the administration of 5-fluorouracil to a subject with cancer due to nickel was reported by Rybnikov and Volkova to have increased the elimination of nickel from the body and to have lowered the nickel concentration in the blood and some of the organs. For practical purposes, chemotherapy for nickel carcinogenesis has been limited to studies in experimental animals. Furst and his colleagues induced fibrosarcomas in Fischer-344 rats by intramuscular implantations of nickel powder. The fibrosarcomas that developed were transplanted to host rats of the same strain. After the growth pattern was established, the rats were treated with a number of diverse chemotherapeutic agents. Of the agents studied, only N-methylformamide exhibited antitumorigenic activity.

Recent studies have been undertaken in our laboratory in which nickel subsulfide was implanted in the thigh muscles of four-month old Fischer rats with the purpose of inducing sarcomas and ascertaining the possible antitumorigenic effectiveness of Dithiocarb. Forty-nine rats were implanted according to Gilman’s procedure and 24 of the group were treated with Dithiocarb administered parenterally; 25 were untreated. Of the untreated rats, 84 percent developed rhabdomyosarcomas whereas only 50 percent of the treated rats developed tumors. In Gilman’s studies, the incidence of sarcomas from nickel subsulfide implantations was 80 percent. Although the number of rats in our study was small, the studies suggest that the induction of rhabdomyosarcoma in rats from intramuscular implantations of nickel subsulfide may be partially inhibited by the administration of Dithiocarb. On the basis of these observations, consideration might thus be given to the administration of Dithiocarb periodically in patients with prostheses who develop a hypersensitivity to nickel and have the potential to develop malignant tumors.

Treatment of Nickel Dermatitis and Eczema

During the past five years, noteworthy advances have been made in the treat-

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**Table IV**

<table>
<thead>
<tr>
<th>Treatment of Acute Nickel Carbonyl Poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or doubtful exposure (Urine Ni &lt; 10 µg/dl)</td>
</tr>
<tr>
<td>Give 2 gm Dithiocarb orally in divided doses (4 hour period)</td>
</tr>
<tr>
<td>Moderately severe to severe exposure (Urine Ni &gt; 10 µg/dl)</td>
</tr>
<tr>
<td>Give Dithiocarb orally as follows:</td>
</tr>
<tr>
<td>First day:</td>
</tr>
<tr>
<td>2.0 gm (10 - 0.2 g capsules) 0 hours</td>
</tr>
<tr>
<td>1.0 gm (5 - 0.2 g capsules) 4 hours</td>
</tr>
<tr>
<td>0.6 gm (3 - 0.2 g capsules) 8 hours</td>
</tr>
<tr>
<td>(0.4 gm (2 - 0.2 g capsules) 16 hours</td>
</tr>
<tr>
<td>Subsequent days: 0.4 gm every 8 hours</td>
</tr>
<tr>
<td>Maintenance of adequate oxygenation</td>
</tr>
<tr>
<td>Cortisol administration for adrenal cortical insufficiency</td>
</tr>
</tbody>
</table>

**Table V**

<table>
<thead>
<tr>
<th>Experimental Chemotherapy in Nickel Carcinogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-methylformamide - Antitumorigenic activities</td>
</tr>
<tr>
<td>exhibited to nickel-induced transplanted fibrosarcomas in rats</td>
</tr>
<tr>
<td>Sodium diethyldithiocarbamate - Partial inhibition of rhabdomyosarcoma induction from i.m. implantation of NiS\textsubscript{2} in rats</td>
</tr>
</tbody>
</table>
TABLE VI
Treatment of Nickel Dermatitis

- Ingestion of diet of low nickel content.
- Oral administration of Dithiocarb (DDC) or Oral administration of Antabuse.
- Topical applications of corticosteroid and/or Dithiocarb preparations.

MENT of skin lesions that result from contact with nickel. Christensen and Moller in 1975 showed that the ingestion of nickel in amounts present in the normal diet caused an exacerbation of dermatitis in nickel-sensitive patients. This observation obviously suggested that patients suffering from nickel dermatitis be placed on a diet of low nickel content and be given a nickel chelating agent. By using a low nickel diet, Kaaber, Veien, and Tjell obtained improvement in hand eczema in nine out of 17 nickel-sensitive patients. Menne and Kaaber also treated a patient with pompholyx due to nickel allergy with Dithiocarb and Antabuse and obtained improvement. Spruit et al used dithiocarbamate therapy in one patient. More recently, Menne, Kaaber, and Tjell treated 11 patients with chronic nickel hand dermatitis with Antabuse and observed a clearing of the dermatitis in eight of them. Since Dithiocarb is categorized as an experimental drug and was unobtainable in Denmark, the authors used tetraethylthiuramdisulfide (Antabuse) in its place. Antabuse is a reasonable substitute since in the metabolism of Antabuse, Domar and associates have shown that two molecules of Dithiocarb are formed as a reduction product. As shown in table V, Antabuse is also a chelating agent that is partially effective in the treatment of acute nickel carbonyl poisoning. Based on the observations of the Danish workers, the suggested treatment for nickel dermatitis is outlined in table VI. In addition to the ingestion of a diet of low nickel content, it is our suggestion that courses of Dithiocarb or Antabuse be given over a seven day period, followed by a week without medication. It is believed that this intermittent type of administration of Dithiocarb might diminish any side effects and aid in the evaluation of the therapeutic response. It should be noted, however, that continuous administration of Dithiocarb for a period of 90 days in rats and dogs failed to elicit any noteworthy side effects and that the concentrations of serum calcium, magnesium, and iron remained within the normal ranges of values. In addition, topical applications of corticosteroids and Dithiocarb preparations are believed to be therapeutically helpful.

In table VII is given a list of foods and beverages with nickel concentrations over one part per million. Tea and cocoa are beverages with high nickel content. In general, the foods with the highest nickel content are cereals and green, leafy vegetables. It is suggested that patients with nickel dermatitis curtail the ingestion of the listed foods and beverages.

TABLE VII
Foods and Beverages with Nickel Content Above 1 PPM

<table>
<thead>
<tr>
<th>Food</th>
<th>Fresh Wt.</th>
<th>Dry Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baking powder</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>Tea (orange pekoe)</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Buckwheat</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Cocoa</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Gelatin</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Pepper (black)</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Wheaties</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Rye</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Oats (unpolished)</td>
<td>1.7-2.6</td>
<td></td>
</tr>
<tr>
<td>Rice (unpolished)</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Salmon</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Oysters</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

summary

Earlier in this century, the opinion was held that excepting for nickel carbonyl, nickel and nickel salts were not harmful to humans. In fact, until World War II, nickel salts were extensively used medicinally for the treatment of a variety of disorders.
CHELATION THERAPY IN NICKEL POISONING

During the past two or three decades, however, it has gradually become evident that, in addition to nickel carbonyl, exposure to other nickel compounds may be deleterious to health.

Dithiocarb (sodium diethyl dithiocarbamate) has proved to be a specific antidote for acute poisoning from the inhalation of nickel carbonyl. For the treatment of skin lesions caused by contact with nickel, favorable response has been observed by the ingestion of Dithiocarb combined with a low-nickel diet. Experimental studies suggest that chelation therapy with Dithiocarb should be considered for the treatment of tumors arising from implantation of metallic prostheses.

References


28. National Research Council. Committee on Medical and Biologic Effects of Environmental


