A Review of the Metabolism and Toxicology of Nickel*†

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ABSTRACT

Although nickel is an essential element for animal nutrition, the physiological role of nickel is not yet established. Pathological alterations of nickel metabolism are recognized in several human diseases. The diverse clinical manifestations of nickel toxicology include: (1) acute pneumonitis from inhalation of nickel carbonyl, (2) chronic rhinitis and sinusitis from inhalation of nickel aerosols, (3) cancers of nasal cavities and lungs in nickel workers, and (4) dermatitis and other hypersensitive reactions from cutaneous and parenteral exposures to nickel alloys. The toxicity, carcinogenicity and embryotoxicity of nickel compounds in experimental animals are reviewed in this article, and consideration is given to the therapeutic use of chelating drugs in nickel poisoning.

Introduction

The objective of this paper is to summarize recent contributions to the metabolism and toxicology of nickel. This manuscript is intended to bring up-to-date the comprehensive monograph on medical and biologic effects of nickel that was published in 1975 by the Panel on Nickel of the National Academy of Sciences.144

Metabolism and Pathophysiology of Nickel

NUTRITIONAL ESSENTIALITY

Studies from 1970 to 1974 by Nielsen et al,90,91 Sunderman et al,153 and Anke et al2 suggested, but did not conclusively demonstrate, that nickel might be an essential element for nutrition of experimental animals. The nutritional essentiality of nickel has recently been unequivocally revealed by investigations of Schnegg and Kirchgessner.68,69,114–117 These investigators have produced a nickel deficiency in rats associated with retarded growth115 and reduction of blood hemoglobin concentrations, hematocrit values and erythrocyte counts.114 Schnegg and Kirchgessner116,117 have shown that nickel

* Supported by research grants from the Energy Research and Development Administration (#E(11-1)-3140) and the National Institute of Environmental Health Sciences (#ES 01337-01).
† Presented at the International Symposium on Clinical Chemistry and Chemical Toxicology of Metals, Monte Carlo, Monaco, March 4, 1977. This paper will be included in modified form in the proceedings of that Symposium.
deprivation profoundly impairs intestinal absorption of iron and thereby causes anemia. Moreover, Kirchgessner and Schnegg have found that nickel deficiency is attended by diminished activities of malate dehydrogenase and glucose-6-phosphate dehydrogenase in rat hepatocytes.

**Nickel Metalloproteins**

In 1966, Himmelhoch et al fractionated human serum by column chromatography, and they isolated a metalloprotein which is rich in nickel and which does not contain detectable amounts of other trace metals. In 1971, Nomoto et al isolated a similar nickel-containing protein from rabbit serum which they named “nickeloplasmin.” Immunologic studies have indicated that rabbit serum nickeloplasmin reacts as an α1-macroglobulin. The nickel that is present in nickeloplasmin is not readily exchangeable with Ni(II) in vivo or in vitro. Haupt et al have isolated a 9.5S-α1-glycoprotein which is present in human serum and which has strong binding for Ni(II). The relationship between the Ni-binding-9.5S-α1-glycoprotein and serum nickeloplasmin is obscure, but it is possible that nickeloplasmin may represent a complex of the 9.5S-α1-glycoprotein with serum α1-macroglobulin. Interest in nickel metalloproteins has been stimulated by the recent discovery of Dixon et al that jack bean urease is a nickel metalloenzyme. Several animal enzymes are currently under scrutiny as possible nickel metalloenzymes. One of these enzymes, formylglycineamidophosphoribosyltransferase (“FGAR transferase”), has been isolated by J. M. Buchanan at the Massachusetts Institute of Technology and has been subjected to nickel analyses in our laboratory. Our analyses have shown that the purified FGAR transferase does not contain a significant amount of nickel.

**Nickel Binding to Albumins**

Several investigations have shown that albumin is the principal Ni(II)-binding protein in human, bovine, rabbit and rat serums. Ni(II) competes with Cu(II) for binding within a square planar ring that is created by (1) the terminal amino group, (2) the first two peptide nitrogen atoms at the N-terminus of the albumin molecule and (3) the imidazole nitrogen of the histidine-residue which is located at the third position from the N-terminus. The presence of histidine at the third position of the albumin molecule appears to be a key feature of the binding site. Thus canine and porcine albums contain tyrosine in lieu of histidine at the third position, and these albums have less affinity for Ni(II) than do the albums for other species (table I).

It is interesting to note that Lau et al synthesized diglycylhistidine-N-methylamide as a biochemical analog of the primary binding site of human albumin for Ni(II) and Cu(II), and they proposed that this tripeptide might serve as a drug for chelation of these metals. Horak et al tested the antidotal efficacy of diglycylhistidine-N-methylamide in rats which received parenteral injection of NiCl₂, and they found that the tripeptide possessed the antidotal property for which it was specifically designed. However, the effectiveness of diglycylhistidine-N-methylamide as a chelating drug appeared to be limited by its rapid rate of catabolism.

**Intracellular Nickel-Binding Proteins**

Little is known about intracellular Ni(II)-binding proteins. Insofar as the authors can ascertain, there is no evidence that Ni(II) binds to metallothionein and related cysteine-rich proteins in the cytosol of mammalian liver and kidney. Thus, E. Sabbioni (personal communica-
tion, 1975) did not observe *in vivo* binding of $^{63}$Ni(II) to metallothionein in rats after induction of the protein by an injection of Cd(II). According to Sabbioni and Marafante, Piotrowska and Szymenska, parenteral administration of Ni(II) to rats does not influence the concentrations of metallothionein-like proteins in liver and kidney. Attempts to isolate and to characterize Ni(II)-binding proteins in the ultracentrifugal supernatant fractions of liver and kidney homogenates from $^{63}$Ni(II)-treated rats are currently in progress in our laboratory.

**ULTRAFILTRABLE NICKEL-BINDING SUBSTANCES**

Ultrafiltrable Ni(II)-binding ligands play an important role in (1) extracellular transport of nickel, (2) intracellular binding of nickel, and (3) excretion of nickel in urine and bile. Asato et al. used autoradiography of thin layer chromatograms to demonstrate five distinct $^{63}$Ni-complexes in serum ultrafiltrates from rabbits that had received intravenous injection of $^{63}$NiCl$_2$. The ultrafiltrable $^{63}$Ni(II)-complexes were rapidly cleared from the rabbit serum and eliminated in urine and bile. The identity of the ultrafiltrable Ni(II)-ligands in serum has not been established, but the ligands react with ninhydrin to yield purple-colored compounds. Preliminary experiments suggest that $^{63}$Ni(II) may be complexed with cysteine, histidine and aspartic acid, either singly or as mixed-ligand species.

**NICKEL METABOLISM IN HEALTHY PERSONS**

According to Schroeder et al., the dietary intake of nickel by adults in the USA in 1962 ranged from approximately 300 to 600 $\mu$g per day. Most of the nickel that is ingested orally is excreted in the feces. Horak and Sunderman found that the fecal excretion of nickel in 10 healthy adults averaged 259 (SD ± 126) $\mu$g per day. The normal fecal excretion of nickel is approximately 100 times greater than the normal urinary excretion of nickel. Reference values for nickel in body fluids and excreta from healthy adults who reside in the vicinity of Hartford, Connecticut are listed in table II, based upon measurements in the author’s laboratory.

The mean concentration of nickel in sweat from healthy men is approximately 20 times greater than the mean concentration of nickel in urine. Under conditions of profuse sweating, appreciable amounts of nickel are excreted in sweat, which may be responsible for the diminished concentrations of serum nickel which have been reported by Szadkowski et al. in workmen who were chronically exposed to extreme heat. Schroeder and Nason, Nechay and Sunderman, and Katz et al. have performed measurements of nickel in hair samples from healthy subjects. Considerable disparities exist between the concentrations of nickel in hair that have been found by these workers, presumably as a result of differences in the techniques for collecting and washing the hair samples. Based upon animal experiments, Scheiner et al. have recently concluded that hair is not a valid biopsy tissue for the assessment of nickel ingestion.

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**TABLE I**

<table>
<thead>
<tr>
<th>Species</th>
<th>1st Assoc. Constant</th>
<th>Amino Acid Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>$6 \times 10^5$</td>
<td>NH$_2$-Asp-Ala-His-</td>
</tr>
<tr>
<td>Rat</td>
<td>$4 \times 10^5$</td>
<td>NH$_2$-Glu-Ala-His-</td>
</tr>
<tr>
<td>Pig</td>
<td>$1.6 \times 10^5$</td>
<td>NH$_2$-Asp-Thr-Tyr-</td>
</tr>
<tr>
<td>Dog</td>
<td>$0.5 \times 10^5$</td>
<td>NH$_2$-Glu-Ala-Tyr-</td>
</tr>
</tbody>
</table>
**TABLE II**

Nickel Concentrations in Specimens from Healthy Residents of Hartford

<table>
<thead>
<tr>
<th>Sample</th>
<th>Number of Subjects</th>
<th>Nickel Concentrations in Body Fluids and Excreta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Blood</td>
<td>17(10°, 7%)</td>
<td>4.8 ± 1.3</td>
</tr>
<tr>
<td>Serum</td>
<td>80(37°, 43%)</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>Urine</td>
<td>50(24°, 28%)</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td>Saliva</td>
<td>20(14°, 6%)</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td>Feces</td>
<td>10(6°, 4%)</td>
<td>14.2 ± 2.7</td>
</tr>
<tr>
<td>Sweat</td>
<td>33°</td>
<td>258 ± 126</td>
</tr>
<tr>
<td>Hair</td>
<td>20(13°, 7%)</td>
<td>52 ± 36</td>
</tr>
<tr>
<td></td>
<td>0.22 ± 0.08</td>
<td>0.13-0.51</td>
</tr>
</tbody>
</table>

**ENVIRONMENTAL EFFECTS OF NICKEL METABOLISM**

McNeely et al\(^82\) compared nickel concentrations in serum and urine specimens from healthy adult inhabitants of Hartford, CT (a city with relatively low environmental concentrations of nickel) with nickel concentrations in specimens from a matched group of adult inhabitants of Sudbury, Ontario, Canada (a city which is the site of the largest nickel mines in North America). None of the subjects had occupational exposure to nickel. In contrast to the values for nickel in serum and urine of the Hartford inhabitants (table II), the inhabitants of Sudbury had mean concentrations of serum nickel of 4.6 ± 1.4 µg per liter (range = 2.0 to 7.3) and mean excretions of nickel in urine of 7.9 ± 3.7 µg per day (range = 2.3 to 15.7). These measurements provided the first direct evidence that analyses of nickel in serum and urine could serve as laboratory indices of environmental exposures to nickel.

**PATHOPHYSIOLOGY OF NICKEL METABOLISM IN MAN**

Pathophysiologival alterations of nickel metabolism have been observed in certain human diseases. D'Alonzo and Pell\(^81\) and Sunderman et al\(^154\) reported increased concentrations of nickel in serum from patients after acute myocardial infarction. Data for nickel concentrations in serum specimens obtained from a total of 73 patients at various intervals following onset of myocardial infarction are summarized in table III, based upon the reports of Sunderman et al\(^154\), McNeely et al\(^83\), and additional cases that have recently been studied by the author. Based upon unpublished studies in the author's laboratory, it seems probable that the hypernickelemia in myocardial infarction is a secondary manifestation of leukocytosis and leukocytolysis. No correlation has been observed between serum nickel concentration and serum activity of creatine kinase or serum activity of the cardiac isoenzyme of lactate dehydrogenase. McNeely et al\(^83\) found hypernickelemia in patients with acute stroke and extensive thermal burns, and they observed hyponickelemia in patients with hepatic cirrhosis or uremia, as a consequence of marked hypoalbuminemia.

**Nickel Carbonyl Poisoning**

**CLINICAL MANIFESTATIONS**

Nickel carbonyl, Ni(CO)\(_4\), a volatile, colorless liquid was discovered in 1890
by Mond et al. and its extraordinary toxicity was quickly recognized by McKendrick and Snodgrass. The first severe cases of nickel carbonyl poisoning in industrial workers occurred in 1902, soon after construction of the Mond nickel refinery in Clydach, Wales. The clinical manifestations of nickel carbonyl poisoning have been thoroughly described by Sunderman, von Ludewigs and Thiess and Vuopala et al and will be briefly summarized in this paper.

Accidental exposure of workers to inhalation of Ni(CO)₄ usually produces mild, non-specific, immediate symptoms, including nausea, vertigo, headache, dyspnea and chest pain. These initial symptoms usually disappear within a few hours. After 12 to 36 hours, and occasionally as long as 5 days after exposure, severe pulmonary symptoms develop, with cough, dyspnea, tachycardia, cyanosis and profound weakness. Death has occurred from 4 to 13 days after the exposure to Ni(CO)₄ and has usually been the result of diffuse interstitial pneumonitis and cerebral hemorrhage or edema. In addition to pathologic lesions in the lung and brain, lesions have been reported in the liver, kidneys, adrenal glands and spleen of diseased workers. In patients who recover from acute Ni(CO)₄ poisoning, there is usually a protracted convalescence, owing to pulmonary insufficiency.

**Pathological Reactions to Ni(CO)₄**

Studies of the pathologic reactions of experimental animals to Ni(CO)₄ exposures have been performed by Sunderman et al and Hackett and Sunderman. The pulmonary parenchyma has consistently been found to be the principal target tissue of Ni(CO)₄ toxicity, regardless of the route of administration. Type I alveolar cells (membranous pneumocytes) are primarily damaged by Ni(CO)₄, but type II alveolar cells (granular pneumocytes) are also affected. The biochemical pathology of Ni(CO)₄ injury of the lungs has recently been discussed by Witschi and Côté.

**Metabolism of Ni(CO)₄**

Investigations of the metabolism of Ni(CO)₄ in rats, and gas chromatographic measurements of

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Number</th>
<th>Serum Nickel (μg/l)</th>
<th>Ni &gt; 4.2 μg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>80</td>
<td>2.6 ± 0.9</td>
<td>0.8-5.2</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 hours</td>
<td>44</td>
<td>4.0 ± 2.1 *</td>
<td>0.2-8.9</td>
</tr>
<tr>
<td>13-24 hours</td>
<td>46</td>
<td>3.9 ± 2.4 *</td>
<td>0.2-10.8</td>
</tr>
<tr>
<td>25-48 hours</td>
<td>64</td>
<td>3.5 ± 2.3 *</td>
<td>0.2-11.4</td>
</tr>
<tr>
<td>49-72 hours</td>
<td>57</td>
<td>3.1 ± 2.1</td>
<td>0.2-7.7</td>
</tr>
<tr>
<td>72-96 hours</td>
<td>52</td>
<td>3.2 ± 1.8</td>
<td>0.2-8.7</td>
</tr>
<tr>
<td>96-120 hours</td>
<td>23</td>
<td>2.5 ± 2.8</td>
<td>0.2-12.7</td>
</tr>
</tbody>
</table>

* P < 0.05  * P < 0.005  * P < 0.001 vs Healthy Controls
Ni(CO)₄ in blood and breath of rats have shown that Ni(CO)₄ can cross the aveolar membranes in either direction without metabolic alteration.⁶³,¹⁵₅,¹⁵₆ During 2 to 4 hours after exposure of rats or rabbits to Ni(CO)₄, the lung is a major excretory organ for Ni(CO)₄.⁸⁵,¹⁵₆ Thereafter, Ni(CO)₄ is progressively oxidized within erythrocytes and other cells to liberate (1) Ni(II) which is excreted in the urine and (2) carbon monoxide which is eliminated in the expired breath.⁶⁵,⁸⁵,¹⁵₅,¹⁵₆

**INDICES OF SEVERITY OF Ni(CO)₄ POISONING**

Mikheyev⁸⁵ has reported that the severity of Ni(CO)₄ poisoning can best be judged by the concentration of nickel in whole blood during the first minutes and hours after exposure. After a few hours, Mikheyev⁸⁵ has reported that the concentration of nickel in urine serves as the best criterion of severity of Ni(CO)₄ poisoning. Based upon observations of workers who were accidentally exposed to inhalation of Ni(CO)₄, Sunderman and Sunderman¹³⁷ classified human exposures as (1) *mild* if the initial 8-hour collection of urine has a nickel concentration <100 μg per liter, (2) *moderately severe* if the nickel concentration in the initial 8-hour urine collection is >100 μg per liter but <500 μg per liter, and (3) *severe* if the nickel concentration is >500 μg per liter.

**CHELATION THERAPY OF Ni(CO)₄ POISONING**

Sunderman and Sunderman¹³⁷ recommended that patients in the *moderately severe* and *severe* categories of Ni(CO)₄ exposure should be treated immediately by administration of a chelating drug, sodium diethyldithiocarbamate ("Dithiocarb"). Sodium diethyldithiocarbamate has been used successfully for therapy of numerous workers who have been poisoned by Ni(CO)₄.¹³⁰,¹³³ Baselt et al⁸ have recently compared the antidotal efficacies of sodium diethyldithiocarbamate (DDC), d-penicillamine (d-Pen) and triethylenetetramine (TETA) as antidotes for acute poisoning of rats by inhalation of Ni(CO)₄. The chelating drugs were each administered by *im* injection in dosages equivalent to 0.6 times their respective LD₅₀ values. Illustrative data are given in table IV to demonstrate that

### TABLE IV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interval (min)</th>
<th>Ni(CO)₄* (mg Ni/l)</th>
<th>Dosage (mM/kg, i.p.)</th>
<th>Mortality Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>10 Before</td>
<td>3.0</td>
<td>--</td>
<td>33/33 (100%)</td>
</tr>
<tr>
<td>DDC</td>
<td>&quot; &quot;</td>
<td>&quot; &quot;</td>
<td>4.1</td>
<td>1/28 (4%)</td>
</tr>
<tr>
<td>d-Pen</td>
<td>&quot; &quot;</td>
<td>&quot; &quot;</td>
<td>15.6</td>
<td>10/26 (38%)</td>
</tr>
<tr>
<td>Teta</td>
<td>&quot; &quot;</td>
<td>&quot; &quot;</td>
<td>1.4</td>
<td>22/26 (85%)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>10 After</td>
<td>1.5</td>
<td>--</td>
<td>19/26 (73%)</td>
</tr>
<tr>
<td>DDC</td>
<td>&quot; &quot;</td>
<td>&quot; &quot;</td>
<td>4.1</td>
<td>2/26 (8%)</td>
</tr>
<tr>
<td>d-Pen</td>
<td>&quot; &quot;</td>
<td>&quot; &quot;</td>
<td>15.6</td>
<td>4/26 (15%)</td>
</tr>
<tr>
<td>Teta</td>
<td>&quot; &quot;</td>
<td>&quot; &quot;</td>
<td>1.4</td>
<td>6/26 (23%)</td>
</tr>
</tbody>
</table>

* Inhalation of Ni(CO)₄ in air for 15 min.

† Mortality within 2 weeks
the antidotal efficacy of sodium diethylatedithiocarbamate was greater than either of the other chelating drugs.

**HYPERGLYCEMIA INDUCED BY Ni(CO)₄**

Tseretili and Mandzhavidze\(^{170}\) reported hyperglycemia and glucosuria in patients with Ni(CO)₄ poisoning. This finding has been confirmed by L. Morgan (personal communication, 1974). An investigation in the author's laboratory\(^{163}\) has shown that exposure of rats to inhalation of Ni(CO)₄ also induces transient hyperglycemia. The hyperglycemia is maximal at 0.5 and 1 hour after the onset of exposure to Ni(CO)₄, and the magnitude of the hyperglycemia is directly related to the atmospheric concentration of Ni(CO)₄ (table V). Although the pathogenesis of the acute hyperglycemia induced by Ni(CO)₄ has not been established, it is presumably similar to the mechanism of hyperglycemia produced by inhalation or parenteral injection of Ni(II) compounds, as will be discussed subsequently.

**MOLECULAR TOXICOLOGY OF Ni(CO)₄**

The molecular mechanisms of Ni(CO)₄ poisoning have been studied in several investigations.\(^{9,10,139–142,147,150}\) Sunderman has proposed that (1) the immediate toxic effects of Ni(CO)₄ may be mediated by acute inhibition of ATPase in target tissue,\(^{142}\) and (2) the delayed toxic effects of Ni(CO)₄ may result from inhibition of RNA polymerase activity.\(^{10,147}\) Sunderman et al\(^{139–141,150}\) have shown that Ni(CO)₄ has an inhibitory effect on induction of several enzymes in livers of rats, including phenothiazine induction of arylhydrocarbon hydroxylase,\(^{139}\) phenobarbitol induction of aminopyrine demethylase\(^{150}\) and cortisone induction of tryptophan pyrrolase.\(^{140}\) These findings may be a secondary manifestation of impaired synthesis of RNA (table VI). Administration of Ni(CO)₄ to rats produces atypical segregation of the granular and fibrillar components of nucleoli in hepatocytes,\(^{38}\) which is consistent with a toxic effect of Ni(CO)₄ upon nucleolar synthesis of RNA.

**DETECTION OF Ni(CO)₄**

Stedman and Tammaro\(^{126}\) have developed a novel apparatus for quantitative analysis of Ni(CO)₄ in air by means of chemiluminescence. The chemiluminescent Ni(CO)₄ detector is based upon the reaction between Ni(CO)₄ and ozone, in the presence of excess carbon

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**TABLE V**

Effects of Ni(CO)₄ on Plasma Glucose in Rats

<table>
<thead>
<tr>
<th>Ni(CO)₄* (mg Ni/l)</th>
<th>No. of Rats</th>
<th>Plasma Glucose Concentrations (mg/dl)^†</th>
<th>0.5 hr</th>
<th>1 hr</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>20</td>
<td>111 ± 15</td>
<td>110 ± 13</td>
<td>104 ± 14</td>
<td></td>
</tr>
<tr>
<td>0.45</td>
<td>19</td>
<td>141 ± 15†</td>
<td>130 ± 16</td>
<td>107 ± 15</td>
<td></td>
</tr>
<tr>
<td>0.77</td>
<td>20</td>
<td>171 ± 28‡</td>
<td>153 ± 32*</td>
<td>108 ± 21</td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td>20</td>
<td>162 ± 22*</td>
<td>189 ± 25‡</td>
<td>136 ± 17</td>
<td></td>
</tr>
</tbody>
</table>

* Inhalation of Ni(CO)₄ in air for 15 min; Interval after initiation of inhalation of Ni(CO)₄; ‡ Mean ± SD; * P < 0.001 vs Controls
TABLE VI
Acute Hepatic Effects of i.v. Ni(CO)_4 in Rats*

<table>
<thead>
<tr>
<th>Experimental System</th>
<th>% of Controls (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typtophan Pyrroless Activity After Cortisone Induction</td>
<td>72 ± 7†</td>
</tr>
<tr>
<td>Arylhydrocarbon Hydroxylase Activity After Phenothiazine Induction</td>
<td>45 ± 8†</td>
</tr>
<tr>
<td>Cytochrome P450 After Phenobarbital Induction</td>
<td>48 ± 5†</td>
</tr>
<tr>
<td>¹⁴C-Leucine Uptake into Microsomal Proteins</td>
<td>82 ± 6†</td>
</tr>
<tr>
<td>¹⁴C-Orotate Uptake into RNA in vivo</td>
<td>25 ± 7†</td>
</tr>
<tr>
<td>RNA Polymerase Activity in Nuclei</td>
<td>40 ± 7†</td>
</tr>
<tr>
<td>RNA Synthesis by Chromatin-RNA Polymerase in vitro</td>
<td>49 ± 6†</td>
</tr>
</tbody>
</table>

* Ni(CO)_4, 2.2 mg/100g, i.v., 6 to 28 hours before sacrifice
† P < 0.01 vs Controls

monoxide, to yield an excited molecule of nickel oxide. As the excited molecule of nickel oxide descends to the ground state, a photon (λ ≈ 540 nm) is emitted, which can be detected by a photomultiplier detector. This instrument is specific for nickel carbonyl, and it furnishes a detection limit of approximately 10 parts per trillion in air. The recorder response of the Ni(CO)_4 detector is linear from 20 parts per trillion to 100 parts per billion. By use of this apparatus, Stedman and Tammaro²⁶ have shown that traces of Ni(CO)_4 in air do not immediately decompose, as was previously believed. Instead, Stedman and Tammaro²⁶ have found that Ni(CO)_4 in air decays by first-order kinetics, with a half-life of approximately 0.5 hours. The chemiluminescent Ni(CO)_4 detector may prove to be more convenient than gas chromatography¹⁵⁵ as a means for rapid and definitive diagnosis of Ni(CO)_4 poisoning by measurement of Ni(CO)_4 in expired breath of exposed persons.

Nickel Carcinogenesis

CANCER IN NICKEL REFINERY WORKERS

The carcinogenicity of nickel compounds in industrial workers has been comprehensively reviewed in several publications.⁴, ³⁰, ¹⁴⁴⁻¹⁴⁶ Increased incidences of cancers of the lung and nasal cavities have been documented by epidemiological investigations of nickel refinery workers in Wales,²⁶, ²⁷ Canada,⁷⁷, ¹⁵⁹ Norway¹⁰² and Russia.¹⁰⁹ The present authors maintains a tabulation of respiratory cancers that have occurred in workers who were exposed to nickel compounds in industrial operations. As of March, 1977, this tabulation included 447 cases of lung cancer and 143 cases of cancers of the nose and paranasal sinuses. In addition to increased risk of respiratory tract cancers, increased risk of laryngeal cancers has been found in Norwegian nickel refinery workers¹⁰² and increased risks of gastric carcinomas and soft tissue sarcomas have been reported in Russian nickel refinery workers.¹⁰⁹

Three cases of renal cancer occurred among 225 Canadian workers who were involved in electrolytic refining of nickel.¹⁵⁹ Since renal cancer is rare, it seems possible that the renal cancers in these refinery workers might have been related to occupational exposures to nickel compounds. The identity of the nickel compounds that induce cancers in nickel refinery workers remains uncertain, although principal attention has been focused upon (1) insoluble dusts of nickel subsulfide(Ni₃S₂) and nickel oxides (NiO; Ni₂O₃), (2) the vapor of nickel carbonyl (Ni(CO)_4) and (3) soluble aerosols of nickel sulfate, nitrate or chloride (NiSO₄; NiNO₃; NiCl₂).⁴, ¹⁴⁴⁻¹⁴⁶

CANCER IN OTHER NICKEL WORKERS

Tsuchiya¹⁷¹ reported a significant increase in lung cancer incidence among Japanese workers who were exposed to nickel in a variety of industrial operations, but he did not analyze the proportion of these cancers that occurred among refinery workers versus non-refinery workers. To date, there have not been any epidemiological studies of cancer...
mortality among groups of workers who were not employed in nickel refineries, but who nevertheless were chronically exposed to inhalation of nickel compounds (e.g., welders, platers, grinders and chemical workers who employ nickel catalysts for hydrogenation reactions). There have been three previous case reports of cancers of the respiratory tract in workers who were exposed to inhalation of nickel in nickel-plating and grinding operations. An additional patient has recently been examined by the author. This case will be described in detail since it provides additional justification for epidemiological investigations of cancer risks among nickel workers.

**Case Report**

The patient is a 36 year old Caucasian man. He was employed as a tractor driver from age 16 to 24 years. From age 25 (1965) until the present (1977), he has worked in a cutlery factory in Connecticut. From 1965 to 1970, the patient was engaged in a nickel-stripping process, in which he dipped small nickel-plated items (such as teapots) into hot HCl-HNO₃ at approximately 85°C in order to strip off old nickel plating (e.g., from used hotel utensils) in order to expose the base of copper. The items were then brushed clean and were transported to another room of the factory where the items were replated with nickel. The patient never used a respirator, and he was continually exposed to hot acid fumes from the nickel-stripping tanks. It is notable that the patient had no exposure to chromium, although he was exposed to copper and silver, in addition to nickel. The patient stated that the most noxious aspect of this work was his weekly duty of cleaning out the nickel sludge in the nickel-stripping tanks.

After five years of work in the nickel-stripping process, the patient developed severe symptoms of nasal irritation, and he transferred to work in a hydraulic press room from 1970 to 1973. He returned to work in the nickel-stripping process from 1973 to 1975. During 1975, he worked in a metal grinding room where stainless steel fabrication was performed. In December 1975, the patient developed an infection of the right nostril and sinusitis. These conditions did not respond to therapy, and in March 1976, he was admitted to Middlesex Hospital in Middletown, CT, where a biopsy was performed on a polypoid lesion in the nose. The biopsy revealed an invasive epidermoid carcinoma (figures 1 and 2). The tumor was excised surgically, and there was no evidence of involvement of lymph nodes.

The patient was referred to Yale University Hospital in New Haven, Connecticut for radiation
therapy. He received 6,000 rads by combination orthovoltage and electron therapy in April 1976. The patient developed nose bleeds, infection and a nasal septal defect during radiation therapy. In January 1977, the patient was referred to the University of Connecticut Hospital in Farmington, Connecticut for evaluation. At that time, the nasal lesions had healed, and there was no evidence of recurrent neoplasia. The concentration of nickel in the patient's urine was 1.3 μg per liter, which is within the normal range. This normal concentration of nickel in urine was expected, since the patient had not any significant occupational exposure to nickel for several months. He never consumed alcoholic beverages. He never had any serious illnesses prior to the present nasal cancer problem. There is no family history of cancer. In the author's opinion, there is a strong likelihood that this patient's nasal cancer was caused by occupational exposure to nickel. There is close resemblance between this case and another worker in a cutlery factory who developed cancer of the nasal cavity, as previously reported by Bouraset and Galland.13

**NICKEL CARCINOGENESIS IN ANIMALS**

Cancers have been induced in experimental animals by administration of several nickel compounds by a variety of routes, as summarized in Table VII. Pulmonary carcinomas have developed in rats following inhalation of Ni(CO)₄ and Ni₃S₂.13¹,134 and carcinomas of the cranial sinuses have developed in cats following implantation of Ni₃S₂ discs (J. P. W. Gilman, personal communication, 1970). In most of the studies that are listed in Table VII, the malignant neoplasms developed locally at the site of ex-

**TABLE VII**

Experimental Models of Nickel Carcinogenesis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Animals</th>
<th>Compounds</th>
<th>Routes</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heuper⁵⁶,⁵⁷</td>
<td>Rats &amp; Rabbits</td>
<td>Ni dust</td>
<td>Intraosseous &amp; Intrapleural</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>Heuper⁵⁸</td>
<td>Guinea pigs</td>
<td>Ni dust</td>
<td>Inhalation</td>
<td>Anaplastic &amp; Adenocarcinomas (lungs)</td>
</tr>
<tr>
<td>Sunderman <em>et al</em>¹³¹,¹³⁵</td>
<td>Rats</td>
<td>Ni(CO)₄</td>
<td>Inhalation</td>
<td>Epidermoid, Anaplastic &amp; Adenocarcinomas (lung)</td>
</tr>
<tr>
<td>Gilman¹³</td>
<td>Rats &amp; Mice</td>
<td>Ni₃S₂ dust</td>
<td>Intramuscular</td>
<td>Rhabdomyosarcomas</td>
</tr>
<tr>
<td>Heath <em>et al</em>¹⁴³,¹⁴⁴</td>
<td>Rats</td>
<td>Ni dust</td>
<td>Intramuscular</td>
<td>Rhabdomyosarcomas</td>
</tr>
<tr>
<td>Furst <em>et al</em>²²,²¹</td>
<td>Rats &amp; Hamsters</td>
<td>Nickelocene</td>
<td>Intramuscular</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>J.P.W. Gilman*</td>
<td>Cats</td>
<td>Ni₃S₂ discs</td>
<td>Sinus implants</td>
<td>Epidermoid &amp; Adenocarcinomas; Sarcomas</td>
</tr>
<tr>
<td>Lau <em>et al</em>⁷³</td>
<td>Rats</td>
<td>Ni(CO)₄</td>
<td>Intravenous</td>
<td>Carcinomas &amp; Sarcomas</td>
</tr>
<tr>
<td>Furst &amp; Cassetta¹¹</td>
<td>Rats</td>
<td>Ni dust</td>
<td>Intrathoracic &amp; Intrapitoneal</td>
<td>Mesotheliomas</td>
</tr>
<tr>
<td>Ottolenghi <em>et al</em>²⁸</td>
<td>Rats</td>
<td>Ni₃S₂ dust</td>
<td>Inhalation</td>
<td>Epidermoid &amp; Adenocarcinomas (lung)</td>
</tr>
<tr>
<td>Sosinski¹²⁵</td>
<td>Rats</td>
<td>Ni₂O₃ dust</td>
<td>Intracerebral</td>
<td>Sarcomas &amp; Meningiomas</td>
</tr>
<tr>
<td>Stoner <em>et al</em>¹²⁹</td>
<td>Mice</td>
<td>Ni(C₆H₅O₂)</td>
<td>Intraperitoneal</td>
<td>Adenocarcinomas (lung)</td>
</tr>
<tr>
<td>Jasmin &amp; Riopelle⁶³</td>
<td>Rats</td>
<td>Ni₃S₂ dust</td>
<td>Intrarenal</td>
<td>Adenocarcinomas</td>
</tr>
<tr>
<td>Sunderman <em>et al</em>¹⁵²</td>
<td>Hamsters</td>
<td>Ni₃S₂ dust</td>
<td>Intramuscular</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>Danjanov <em>et al</em>²²²</td>
<td>Rats</td>
<td>Ni₃S₂ dust</td>
<td>Intratesticular</td>
<td>Sarcomas</td>
</tr>
</tbody>
</table>

* Personal Communication, 1970
Exposure, injection, or implantation. However, Stoner et al. have observed pulmonary carcinomas in mice that received repeated intraperitoneal injections of nickel acetate. Therefore, it appears likely that certain nickel compounds may induce tumors at sites that are distant from the point of primary contact. Payne, Gilman, and Sunderman and Maenza have found that Ni₃S₂ is the most highly carcinogenic of the nickel compounds that have been evaluated in experimental animals.

**Molecular Biology of Nickel Carcinogenesis**

The experimental evidence that pertains to the molecular mechanisms of nickel carcinogenesis has been comprehensively reviewed by the author in several articles. In order to avoid repetition of this material in the present paper, readers are asked to consult the most recent of these reviews. Particular attention is directed to the notable discovery that manganese suppresses the carcinogenicity of Ni₃S₂ in rats. In vitro screening tests for malignant transformation in tissue culture cells or mutagenesis in bacteria have not yielded positive results for nickel compounds. However, Ni(II) has been shown by in vitro tests to decrease the fidelity of DNA transcription by DNA polymerase.

**Other Aspects of Nickel Toxicology**

**Nickel Analyses as Indices of Occupational Exposures**

Concerns about the carcinogenic hazards of nickel exposures have stimulated several investigators to perform measurements of nickel concentrations in body fluids of various groups of industrial workers. These studies demonstrated increased nickel concentrations in urine or serum of (1) chemical workers who use Ni(CO)₄, (2) workers in the electrolytic and roasting-smelting departments of a nickel refinery, (3) welders who use nickel-containing electrodes to weld stainless steel, (4) workers in plants that produce nickel-containing pigments and (5) workers in nickel-plating operations. Illustrative data for excretion of nickel in urine from nickel-plating workers are shown in table VIII, based upon a recent study in the author's laboratory. Also included in table VIII are data for excretion of nickel in urine from hydrogenation process workers in a pilot plant for coal gasification. These workers were engaged in use of nickel catalysts for hydrogenation of carbon monoxide and carbon dioxide to yield methane. The mean concentration of nickel in the urine of the coal-gasification workers was only slightly greater than in control workers who had no occupational exposures to nickel. On the other hand, a great increase in the mean concentration of nickel was found in urine of the nickel-plating workers. In the author's opinion, measurements of nickel concentrations in urine provide a practical and reliable index of occupational exposures to nickel.

**Table VIII**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Number</th>
<th>Urine Ni Concentration*</th>
<th>(\mu g/l)</th>
<th>(\mu g/g) Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Workers</td>
<td>15</td>
<td>2.7 ± 1.4</td>
<td>2.5 ± 1.3</td>
<td>(0.7 - 4.0) (0.7 - 5.7)</td>
</tr>
<tr>
<td>Non-exposed Industrial</td>
<td>10</td>
<td>2.8 ± 1.3</td>
<td>2.5 ± 1.0</td>
<td>(0.4 - 4.2) (0.6 - 3.6)</td>
</tr>
<tr>
<td>Ni-Plating Workers</td>
<td>21</td>
<td>28 ± 21(\dagger)</td>
<td>19 ± 15(\dagger)</td>
<td>(5.3 - 66) (3.4 - 62)</td>
</tr>
<tr>
<td>Hydrogenation Process</td>
<td>9</td>
<td>4.2 ± 2.4</td>
<td>3.2 ± 1.6</td>
<td>(0.4 - 7.9) (0.1 - 5.8)</td>
</tr>
</tbody>
</table>

* Mean ± SD, and range in parentheses  \(\dagger\) P < 0.001 vs Hospital Workers
EMBRYOTOXICITY AND TRANSPLACENTAL TRANSPORT OF NICKEL

Recent changes in employment practices in North America and Europe have substantially increased the proportion of women among workers in the nickel industry. As a result, there is growing concern regarding possible embryotoxicity associated with exposures of pregnant women to nickel during early pregnancy. Relevant clinical data are not available, and the only evidence related to embryotoxicity of nickel is derived from animal studies. Schroeder and Mitchener studied three generations of rats that were continually given an unspecified nickel salt in the drinking water (5 ppm). Schroeder and Mitchener observed increased proportions of runts and enhanced neonatal mortality in each of the three generations, compared to control rats. Moreover, they noted a substantial reduction in the mean litter size and a reduced proportion of males in the third generation of the nickel-treated rats.

Ambrose et al administered nickel sulfate to rats for three generations. The nickel sulfate was added to the diet in amounts yielding dietary Ni concentrations of 0, 250, 500 and 1000 ppm. Increased incidence of stillbirths was observed in the first generation at all dietary levels of nickel. At the 1000 ppm level of nickel, decreased body weights of weanlings were observed in all generations. Ferm administered nickel acetate to pregnant hamsters by iv injection on day 8 of gestation at dosages ranging from 0.7 to 10 mg Ni per kg. Ferm found dose-related increases in the number of resorbed embryos, as well as a few unspecified malformations in surviving embryos.

Sunderman et al reported dose-related decreases in the mean weights of surviving pups. No congenital malformations were observed. The findings of Schroeder and Mitchener, Ambrose et al, Ferm and Sunderman et al indicate that administration of nickel to pregnant rodents produces fetal mortality and impairs intrauterine growth (table IX). Sunderman et al also showed that Ni(II) can enter the products of conception after im administration to pregnant rats on the day 8 or 18 of gestation (table X). On the basis of the available data, it appears that the embryotoxic hazards of nickel may be comparable to those that have been recognized for certain other metals, including lead, cadmium and mercury.

CHELATING AGENTS AS ANTIDOTES FOR Ni(II) TOXICITY

As mentioned previously, Baselt et al reported that sodium diethyldithiocarbamate was more effective than d-penicillamine and triethylenetetramine as an antidote for acute Ni(CO)4 poisoning in rats. It is noteworthy that the converse relationship applies to the antidotal efficacy of these chelating agents in acute Ni(II) poisoning. Horak et al found that triethylenetetramine and d-penicillamine were very effective antidotes for Ni(II) toxicity in rats and that sodium diethyldithiocarbamate was much less effective. Sunderman et al administered triethylenetetramine im in rats immediately prior to ip injection of NiCl2 and found that triethylenetetramine greatly reduced the concentrations of Ni in hearts and lungs after 6 hours, compared to the concentrations of Ni in hearts and lungs of rats that only received NiCl2.

HYPERGLYCEMIA INDUCED BY Ni(II)

Clary administered NiCl2 to rats by intraperitoneal and intratracheal injec-
tions and observed a marked transient increase in serum glucose. This finding has been confirmed by Horak and Sunderman,52,53 who have established the dose-response relationships for Ni-induced hyperglycemia. Clary20 and Horak and Sunderman52 observed that Ni-induced hyperglycemia is antagonized by exogenous insulin, and Horak and Sunderman22 reported that the hyperglycemic response to Ni(II) is suppressed but not completely prevented by adrenalectomy or hypophysectomy. Horak and Sunderman53,148 measured concentrations of immunoreactive glucagon in plasmas from rats after ip injection of NiCl2, and they found parallel responses of plasma glucagon and glucose concentrations, suggesting that hyperglucagonemia may be responsible for the acute hyperglycemic response to Ni(II). In the studies of Horak and Sunderman,52,53 ip administration of Ni(II) was attended by hyperinsulinemia, presumably as an adaptive response to hyperglycemia. In contrast, Clary20 noted progressive diminutions in concentrations of plasma insulin following intratracheal administration of NiCl2. Interest in the mechanism of Ni(II)-induced hyperglycemia has been stimulated by the recent report of Saggerson et al108 that Ni(II) possesses an in vitro insulin-like activity on fat-cell membranes in rats, with stimulation of glucose incorporation into fat-cell membranes in rats, with stimulation of glucose incorporation into fat-cell lipids and diminution of lipolysis. Unpublished studies of Horak and Sunderman demonstrate that Ni-induced hyperglycemia in rats is not prevented by current administration of somatostatin.

RENAL ACCUMULATION AND NEPHROTOXICITY OF Ni(II)

Following parenteral administration of 63Ni(II) to rodents, the highest concentrations of 63Ni are consistently found in the kidneys20,100,123,176 Renal excretion is the principal route for elimination of injected 63Ni(II).18,47,97 In view of the renal accumulation and excretion of nickel, Gitlitz et al.36 suspected that administration of soluble nickel compounds to rats might produce renal toxicity. Gitlitz et al.36 found that ip administration of NiCl2 to rats in dosages of 2 to 5 mg Ni per kg body weight caused proteinuria, aminoaciduria (figure 3) and reduction of urea clearance, associated with morphological lesions in the renal glomeruli and tubules. Ni(II)-induced nephrotoxicity in

<table>
<thead>
<tr>
<th>TABLE IX</th>
<th>Embryotoxicity of NiCl2 in Rats*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Dosage of NiCl2 (mg Ni/kg)</td>
</tr>
<tr>
<td>A</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
</tr>
<tr>
<td>D</td>
<td>16</td>
</tr>
</tbody>
</table>

* Injection i.m. on the 8th day of gestation. † Dams were killed on the 20th day of gestation; Mean ± SD. ‡ P < 0.01 vs Controls (Group A)

<table>
<thead>
<tr>
<th>TABLE X</th>
<th>63Ni Concentrations in Rat Tissues*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>Non-Pregnant 20th Day</td>
</tr>
<tr>
<td>Kidney</td>
<td>16.4 ± 3.1</td>
</tr>
<tr>
<td>Lung</td>
<td>2.5 ± 0.7</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>Liver</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Urine Contents</td>
<td>---</td>
</tr>
<tr>
<td>Placenta</td>
<td>---</td>
</tr>
<tr>
<td>Fetuses</td>
<td>---</td>
</tr>
<tr>
<td>Amniotic Fluid</td>
<td>---</td>
</tr>
</tbody>
</table>

* N = 12 (4 rats/group) † 63NiCl2 (12 mg Ni/kg) injected i.m. 24 hr before death; Mean ± SD. ‡ Rats were killed on the specified day of gestation.
Erythrocytosis Induced by Intrarenal Injection of Ni$_3$S$_2$

Jasmin and Solymoss$^{64}$ discovered that administration of nickel subsulfide, Ni$_3$S$_2$, to rats by intrarenal injection produces pronounced erythrocytosis. They observed 1.5 fold increase in blood erythrocyte count and 2.4 fold increase in body erythrocyte mass at 5 months after an intrarenal injection of 10 mg of Ni$_3$S$_2$. These findings have been confirmed by Morse et al.$^{88}$ and they elucidated the dose-response and time-response relationships for Ni$_3$S$_2$-induced erythrocytosis in rats.

Hopfer et al.$^{50}$ showed that induction of erythrocytosis by intrarenal injection is not specific for Ni$_3$S$_2$, but also occurs (to a lesser degree) after intrarenal injection of other nickel compounds. They observed strain-differences in susceptibility of rats to Ni$_3$S$_2$-induced erythrocytosis, and they noted that erythrocytosis did not occur in mice or rabbits after intrarenal injection of Ni$_3$S$_2$. The physiological mechanism of Ni$_3$S$_2$-induced erythrocytosis has not been established, but it is presumed to be related to increased renal production and release of erythropoietin.$^{64,88}$

Respiratory Tract Toxicity of Nickel

Tatarskaya,$^{164}$ Kucharin$^{71}$ and Sushenko and Rafukova$^{158}$ have described chronic rhinitis and nasal sinusitis in workers in electrolytic nickel refineries who were chronically exposed to inhalation of nickel aerosols (e.g., NiSO$_4$). Many of these workers developed anosmia and severe damage to the nasal mucosa, including perforations of the nasal septum. The histological findings in the nasal mucosa of workers in an electrolytic nickel refinery have been reviewed by Torjussen and Solberg.$^{168}$ They found precancerous nasal lesions (atypical epithelial metaplasia) in 16 percent of 92 nickel-exposed workers. No such lesions were observed in a control group of workers. Tolot et al.$^{167}$ and McConnell et al.$^{78}$ have published reports of asthmatic lung disease in workers in nickel plating operations.
Cases of Loeffler's syndrome with nickel hypersensitivity have been described by Arvidsson and Bogg and Sunderman and Sunderman. Bingham et al exposed rats to inhalation of soluble (NiCl₂) and insoluble (NiO) aerosols of nickel at atmospheric concentrations near or below the levels that were considered to be acceptable for occupational exposures of workers. They observed hyperplasia of bronchiolar and bronchial epithelium with peribronchial lymphocytic infiltrates, and a marked increase in mucus production. Bingham et al concluded that the current threshold limit value of 1 mg per m³ for atmospheric concentrations of nickel may be too high.

HAZARDS FROM INTERNAL EXPOSURE TO NICKEL

Nickel dermatitis from external (cutaneous) exposure to nickel alloys was comprehensively reviewed in the report of the Panel on Nickel and, hence, will not be considered in detail in this paper. However, numerous recent papers have drawn attention to the problem of allergy and dermatitis from internal exposures to nickel, owing to the presence of nickel in alloys used for orthopedic prostheses, cardiac pacemaker electrodes, cardiac valve replacements, surgical instruments, steel sutures and intravenous cannulae. The cutaneous reactions to internal exposures to nickel have included urticarial, eczematous and pemphigoid lesions.

These allergic reactions to nickel have often been sufficiently severe to necessitate removal of nickel-containing prostheses. It may be noted that Dube and Fisher reported a patient with hemangioendothelioma of the tibia at the site of a nickel-containing implant that had been retained for 20 years, and McDougall reported a patient who developed a sarcoma of soft tissue of an arm at 30 years after implantation of a steel plate. These reports have aroused concern about allergic hazards and possible long-term neoplastic sequellae of internal exposure to nickel alloys.

LYMPHOCYTE BLAST TRANSFORMATION TEST FOR Ni SENSITIZATION

In 1970, Pappas et al reported that nickel acetate is a potent stimulant for in vitro blast transformation of human peripheral blood lymphocytes. Pappas et al did not note any differences in the response of lymphocytes from nickel hypersensitive and non-sensitive patients. Subsequent studies by Hutchinson et al, Millikan et al, Gimenez-Camarassa et al, and Kim and Schoepf have shown that lymphocyte blast transformation, as evidenced by increased thymidine uptake ratios, is enhanced in cells from nickel-sensitive subjects. Millikan et al found good correlation between the in vitro response of lymphocytes and the results of in vivo patch testing for nickel sensitivity, and they recommended use of blast transformation of lymphocytes as an in vitro test for nickel allergy.

A study of Hutchinson et al demonstrated direct binding of Ni to the cell surface of lymphocytes from sensitive and non-sensitive subjects, and they concluded that Ni-binding to the cells is not per se the stimulus for transformation. Several investigators have recently attempted to employ the leukocyte migration inhibition test to differentiate nickel sensitive and non-sensitive subjects; but the results have been negative or equivocal. Therefore, the lymphocyte blast transformation test remains the only practical in vitro procedure for diagnosis of nickel sensitivity.
NICKEL SENSITIZATION IN EXPERIMENTAL ANIMALS

Experimental sensitization of guinea pigs to nickel has been reported by some investigators, but these findings could not be confirmed by other workers. Recently, Wahlberg has succeeded unequivocally in sensitizing guinea pigs to nickel by two different schedules of intradermal injection of NiSO$_4$. This accomplishment will greatly facilitate experimental study of nickel allergy. Wahlberg predicts that it may soon be feasible to perform passive transfer of nickel allergy in experimental animals.

Summary and Conclusions

Nickel is an essential trace metal for animal nutrition, although the physiological role of nickel has not been established. Pathological alterations of nickel metabolism occur in several common diseases of man, such as acute myocardial infarction and stroke. Clinical concerns about nickel toxicity are focused primarily on (1) acute poisoning from inhalation of nickel carbonyl, (2) chronic rhinitis and sinusitis with anosmia and septal perforations from occupational exposures to aerosols of nickel compounds, (3) cancers of the nasal cavities and lungs in nickel-exposed workers, (4) dermatitis and other hypersensitive reactions to nickel, especially following implantation of nickel-containing prostheses and devices and (5) potential embryotoxicity of nickel in pregnant women who have occupational exposures to nickel compounds.

Measurements of nickel concentrations in urine and serum provide laboratory indices of occupational and environmental exposures to nickel compounds. Sensitive gas chromatographic and chemiluminescent techniques are available for detection and quantitation of nickel carbonyl in exhaled breath, for the specific diagnosis of acute nickel carbonyl poisoning. Human hypersensitivity to nickel can be detected in vitro by the lymphocyte blast transformation test.

Studies in experimental animals have shown that parenteral injections of Ni(II) produce (1) acute transient hyperglycemia and hyperglucagonemia in rats, (2) nephrotoxicity with proteinuria, aminoaciduria and diminished urea clearance in rats, and (3) allergic hypersensitivity in guinea pigs. In addition, intrarenal injection of nickel subsulfide induces marked erythrocytosis with bone marrow hyperplasia in rats. Abundant experimental evidence exists for carcinogenicity in laboratory animals of certain nickel compounds, such as nickel subsulfide and nickel carbonyl. In vitro screening tests for malignant transformation in tissue culture cells or for mutagenesis in bacteria have not yielded positive results for nickel compounds. However, Ni(II) has been shown by in vitro tests to decrease the fidelity of DNA transcription by DNA polymerase.

Sodium diethyldithiocarbamate is the most effective antidote for acute nickel carbonyl poisoning in man and experimental animals. Triethylenetetramine and d-penicillamine are effective as antidotes for acute toxicity of Ni(II) after parenteral administration of nickel chloride to rats.

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