Perspectives on Legionnaires’ Disease in Relation to Acute Nickel Carbonyl Poisoning

The Henry M. Scharf Lecture on Current Affairs*

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The original title given to this presentation was “Acute Nickel Carbonyl Poisoning as a Simulator of Viral Pneumonia.” An attempt was made to avoid the use of the term “Legionnaires’ Disease” since the illness was of limited scope and refers solely to one outbreak affecting merely a fraction of one percent of legionnaires living in Pennsylvania who attended the 1976 Legionnaires’ convention in Philadelphia. Despite our feelings in the matter, the term “Legionnaires’ Disease” has recently attained such common usage that for a discourse on current affairs, the original title has been changed,—albeit with reluctance.

Legionnaires’ Disease has been described as the “medical story of the century.” The public interest in it has led to a congressional investigation,—allegedly the first congressional inquiry into the cause of any disease. The disease has received international news coverage. In fact, during conferences in Europe last fall, there was no difficulty in keeping informed on the subject by reading the articles on Legionnaires’ Disease in the newspapers of Munich, Amsterdam and London. Legionnaires’ Disease has led indirectly to the closing of one of the most beautiful and respected historic hotels in this country (i.e., the Bellevue Stratford Hotel of Philadelphia). It was perhaps indirectly responsible for changes in some of the top positions in the Public Health Service. The magnitude of the medical investigations may be contemplated when it is recognized that extensive studies were undertaken by all of the major federal health agencies, many of the state and local health departments and by the faculties and scientists of many of the academic and industrial institutions throughout this country. The investigations also involved the largest force of Epidemic Intelligence Service officers sent into the field in response to a disease outbreak. No other malady in the history of American medicine has produced such widespread concern.

Most scientific publications nowadays begin with an abstract or a summarization. Therefore, perhaps it might be appropriate to begin this lecture on current affairs by making a summarization of our reasoning in the development of our point of view toward Legionnaires’ Disease. Likewise, at the conclusion of the discussion, a few suggestions are offered for consideration.

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Statement

Although the causative agent for the recent outbreak of respiratory illness associated with Pennsylvania legionnaires is not known with certainty; nevertheless in our opinion, sufficient trustworthy data have been developed to warrant a provisional diagnosis of the probable cause.

The illness affected only legionnaires and guests who attended their convention in Philadelphia between July 21 and 24, 1976 and who visited the Bellevue Stratford Hotel during that period. One hundred and seventy-seven legionnaires were reported to have become ill. This number represents only a small percentage of the several thousand legionnaires and guests who attended the convention. In addition, there were many thousands of bicentennial visitors as well as the normal population in Philadelphia during this same period.², ³

The severity of the illness was not recognized at the time of the convention, and thus the illness appeared to be attended by a delayed response. The first reported death occurred on July 27 and the association of the illness with the Legionnaire convention was not recognized until July 30. It was also observed that the illness was not contagious and that the general population and hotel personnel were unaffected. Moreover, intensive laboratory studies during the early months of the investigations failed to isolate any responsible infectious organism.³⁰

Recently the Center for Disease Control of the federal government announced that a bacteria-like organism of an unknown species was found associated with Legionnaires' Disease and was believed to be the causative agent.¹³, ¹⁹, ²⁵ The raw scientific data that formed the basis of this announcement have not appeared as yet in scientific journals. Therefore, judgment regarding the acceptance or rejection of the findings must await published reports and confirmation of the studies by competent investigators in other institutions. It seems unrealistic, however, that an unknown type of bacteria was capable of singling out Pennsylvania war veterans as hosts and producing in them a disease which, in itself, is not contagious. It is, therefore, understandable that a degree of skepticism has been raised that such an unclassified, strange bacterium was the causative factor.

Since the disease was not contagious and the outbreak was limited to a specific group of persons, it is believed the illness must be attributed to exposure to a toxic agent. Moreover, the symptoms of the illness were primarily respiratory with only secondary gastro-intestinal manifestations and, therefore, it is reasonable to consider that the toxic agent was probably inhaled. Of the toxic inhalants under consideration, nickel carbonyl is the only odorless one of which we are aware that will produce the type of delayed symptomatology, physical findings and lesions that were reported among the affected legionnaires. The onset of severe symptoms from one to ten days after exposure, in our experience, is uniquely characteristic of nickel carbonyl poisoning. * Since the vapor of nickel carbonyl is colorless and odorless, † † victims would not have been able to detect its presence.

* Chemical poisoning from the weed killer, Paraquat (1,1'-dimethyl-4, 4'-bipyridylium dichloride), is also reported to be attended by a delayed response. However, poisoning from Paraquat occurs with the onset of liver and kidney damage and with the occurrence of jaundice and uremia.

† Sometimes described as "slightly musty." On questioning victims of acute nickel carbonyl poisoning, the statement is usually made that they detected no odor.

†† Most lethal gases have distinctive odors and produce immediate physiological responses such as lacrimation, respiratory irritation, vesication, stertoration, narcosis, etc.
or to have become aware of exposure to it. The delayed response, the course of the illness, the symptoms and the physical findings of the victims conform closely to those of acute nickel carbonyl poisoning. It is for these reasons that the possibility was entertained initially that the outbreak might have been caused by exposure to nickel carbonyl.

A confirmed diagnosis of acute nickel carbonyl poisoning is normally established by the finding of high concentrations of nickel in urine and blood during the first few days after exposure. Since urine and blood samples were not saved during this early period, no analyses were obtainable.*

Although the results of nickel analyses on tissues obtained at autopsy from victims of the outbreak have been labelled "inconclusive," owing to the possibility of contamination; nevertheless, the results were also labelled as being certainly "suggestive."† The nickel concentrations in the lungs of five of the six subjects with Legionnaires' Disease were from 45 to 162 micrograms per 100 grams of tissue by dry weight. These values are several fold greater than the concentrations of 3 to 14 micrograms observed in unexposed persons.† If contamination can be completely ruled out, then acute nickel carbonyl poisoning is the only recognized disorder that would yield the high values that were found.

The summarization report of the panel of 12 pathologists assembled by the Center for Disease Control to review the autopsy material reasoned that the alveolar lesions in the lungs were "probably produced by a toxic substance" and that "the possibility that the cause was a virus infection was generally considered to be remote."‡ Furthermore, histopathologic examination of the tissues which we studied also revealed changes which were unusually similar and consistent with those observed in patients known to have died from acute nickel carbonyl poisoning.

In so far as we are aware, no data have been submitted that negate the provisional diagnosis of acute nickel carbonyl poisoning in the outbreak among legionnaires; indeed, all of the available data support this provisional diagnosis. Therefore, pending disclosures of which we are unaware, it is *still our opinion* that Legionnaires' Disease was caused by exposure of the victims to the vapor of nickel carbonyl.

**A Point of View Regarding the Failure to Consider Initially Chemical Poisons and Toxins**

Frequent mention has been made in the news media of the failure of the health authorities to consider exposure to chemicals and toxins in the early investigations of Legionnaires' Disease. This factor may, in part, be attributable to the political environment regarding health matters at the time of the outbreak.

A Public Health Service Act passed in April 1976 authorized the expenditure of 135 million dollars for the establishment and implementation of an emergency national swine influenza immunization program for 1976. The drug manufacturers, however, were reluctant to release

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* Five samples of urine were received in Dr. Sunderman, Jr.'s laboratory on August 19, 1976. These samples were reported to have been collected between July 30 and August 3.‡

† Dr. James R. Chen used a proton induced x-ray emission method for the measurement of nickel and also confirmed the high concentrations of nickel in tissues.†

‡ The panel noted that since the lining cells of the bronchioles were not primarily involved, the toxic agent might have been ingested. However, it should be pointed out that, unlike many poisonous inhalants, nickel carbonyl is not irritating when inhaled and, hence, the lining cells of the bronchioles do not reveal primary damage in acute nickel carbonyl poisoning.
the vaccine unless they were afforded protection against liability suits. The public health officials were understandably engrossed in the problems of mass immunization for swine flu, especially since the wisdom of spending 135 million dollars to vaccinate a population against influenza was being questioned in many parts of the country. On August 10, 1976, the New York Times indicated that Mr. Mathews, Secretary of Health, Education and Welfare, described the situation (i.e., mass immunization) as being in a state of collapse and jeopardized by delays.

There is little doubt that the inference that Legionnaires' Disease might have been the beginning of an epidemic of swine flu was the spark that provided rapid passage of Public Law 94-380 to amend the Influenza Immunization Act. On August 10, 1976, the Senate passed unanimously by voice vote the amendment making the government responsible for defending any lawsuit arising from the immunization program, if the injury was attributed to negligence.

The initial emphasis that the outbreak might be the beginning of an epidemic of swine flu may be understandably attributable in part to the zeal of the public health authorities to have the pending legislation enacted in Congress. The failure to consider chemical poisons and toxins as possible causative factors during the early stages represents a "flaw" in the scientific investigations. If these had been considered, samples of excreta and blood would have been saved for the analyses upon which a confirmed diagnosis might have been established.*

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* Some of the press mentions have been exceptionally critical. To quote one Washington press column: "Had it not been for an eagerness bordering on mania on the part of CDC to find swine flu in Pennsylvania, it is entirely possible that the real cause of whatever snuffed out 29 lives and threatened 150 others might have been ascertained."

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**Brief Résumé of Nickel Carbonyl and Its Toxicity**

It is only within the past three or four decades that the hazards of exposure to nickel and nickel compounds have come to be recognized. The hazards of exposure to lead and arsenic have been known for centuries; however, the hazards of exposure to nickel, which are potentially greater owing to its carcinogenicity, have only been revealed in recent years. In the course of our medical investigations during World War II, it became apparent in 1943 that exposure to nickel and certain of its compounds, notably nickel carbonyl, was a serious health hazard and a handicap to the furtherance of research work in atomic energy. As a consequence, studies were initiated to provide safeguards for the handling of nickel carbonyl during the war, and these studies are still continuing. Obviously, an enormous amount of data has been collected which can only be briefly reviewed at this time.

**Walter Reppe**, a German chemist, made a major contribution in the field of chemistry when he discovered the oxo and related reactions catalyzed by nickel carbonyl. As a result of his work, nickel carbonyl has been introduced into many of the large chemical industrial processes. In addition to the separation of nickel from its ores, one of the important uses is as an intermediate in the synthesis of acrylic esters for the production of certain plastics and paints. It is also employed in nickel-plating operations and as a medium for depositing thin layers of metallic nickel in electronic circuits and magnetic tapes. It is now being used for casting operations and in making dies for machine parts. It is ordinarily prepared for use in organic syntheses by the reaction of certain nickel salts and carbon monoxide at high pressures. Nickel carbonyl may also be formed inadvertently whenever carbon monoxide comes into
contact with any active form of nickel. In this event, the hazards of exposure are increased because the presence of nickel carbonyl lacks any detectable odor to warn of its presence.

Some of the properties of nickel carbonyl are listed in table I. Nickel carbonyl is a clear, colorless liquid which boils at 43° C. and has a vapor pressure of 380 mm of mercury at 25° C. Its high volatility creates a special hazard of exposure by inhalation since the vapor is essentially odorless.

Nickel carbonyl in gaseous form is unstable under atmospheric conditions and, if inhaled, nickel is deposited in active form on the respiratory mucosa.

Nickel carbonyl is one of the most toxic compounds encountered in industrial operations. The American Conference of Governmental Industrial Hygienists in 1971 placed the threshold limit value of nickel carbonyl for eight hours at one part per billion (by comparison, hydrogen cyanide was placed at ten parts per million,—a 10,000 times greater concentration). However, unlike hydrogen cyanide, a lethal exposure to nickel carbonyl is not usually immediately fatal. The LD₅₀ values for a 30 minute exposure to nickel carbonyl for mice, rats and cats are 0.067, 0.24 and 0.19 milligram per liter of air, corresponding to 10, 35 and 28 parts per million, respectively.

### Synopsis of Clinical Observations in Acute Nickel Carbonyl Poisoning

It is suspected that acute nickel carbonyl poisoning may not be too uncommon an occurrence, and that poisoning from it often goes unrecognized. The acute symptoms which follow exposure to nickel carbonyl are listed in table II. They are characteristically of two types,—immediate and delayed.

* LD₅₀ represents that concentration that is lethal for 50 percent of exposed experimental animals.

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### Table I

<table>
<thead>
<tr>
<th>Properties of Nickel Carbonyl Ni(CO)₄</th>
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</thead>
<tbody>
<tr>
<td><strong>Clear, colorless liquid</strong></td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
</tr>
<tr>
<td><strong>Specific gravity</strong></td>
</tr>
<tr>
<td><strong>Boiling point</strong></td>
</tr>
<tr>
<td><strong>Vapor pressure</strong></td>
</tr>
<tr>
<td><strong>Density of vapor</strong></td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
</tr>
<tr>
<td><strong>Cold water 9.8°, 18 ppm</strong></td>
</tr>
<tr>
<td><strong>Odor threshold</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LD₅₀ value (30 min exposure)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouse</strong></td>
</tr>
<tr>
<td><strong>Rat</strong></td>
</tr>
<tr>
<td><strong>Cat</strong></td>
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</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Symptoms of Acute Nickel Carbonyl Poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate</strong></td>
</tr>
<tr>
<td>Mild, non-specific symptoms disappear when subject removed to uncontaminated air</td>
</tr>
<tr>
<td>Headache; dizziness</td>
</tr>
<tr>
<td>Sternal &amp; epigastric pains</td>
</tr>
<tr>
<td>Nausea &amp; vomiting occ.</td>
</tr>
<tr>
<td><strong>Latent</strong></td>
</tr>
<tr>
<td>1 - 5 days</td>
</tr>
<tr>
<td><strong>Delayed</strong></td>
</tr>
<tr>
<td>Constriction in chest</td>
</tr>
<tr>
<td>Chills, sweating</td>
</tr>
<tr>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Unproductive cough</td>
</tr>
<tr>
<td>Muscle pains</td>
</tr>
<tr>
<td>Weakness, fatigue</td>
</tr>
<tr>
<td>Gastro-intestinal symptoms occ.</td>
</tr>
<tr>
<td>Convulsions and delirium - sometimes terminally</td>
</tr>
</tbody>
</table>
ness, sternal and epigastric pains. Some patients become nauseated after exposure and may vomit. Hours after exposure, most of the patients experience a sense of constriction in the chest with concomitant shortness of breath and a dry, hacking, unproductive cough. A universal complaint in the critically ill patients is weakness and fatigue. At times, respiration cannot be sustained without pressure oxygen therapy. Breathing is frequently rapid and shallow. Some critically ill patients may develop neurological symptoms. Two of our patients had terminal convulsions; others became irrational.

Diarrhea and abdominal distention may occur two or more days after exposure. This might suggest that nickel was being excreted by the intestinal tract, similar to the diarrhea that follows arsenic poisoning.

Fever is usually not a prominent finding after acute exposure to nickel carbonyl. Generally, the temperature ranges from 101° to 103°, although higher fever at times has been observed in severe cases. Within recent years, since the therapeutic use of the specific antidote, sodium diethyldithiocarbamate (Dithiocarb), patients with acute nickel carbonyl poisoning survive; hence, the patients do not develop the acute pneumonitis with attendant high fever that is observed in patients who had not received the antidote. When high fever occurs, it represents either a superimposed secondary infection or perhaps an allergic manifestation of nickel in combination with other metals or other agents, such as alcohol. It might be mentioned that many of the cases of Legionnaires' Disease reviewed by the panel of pathologists revealed superimposed secondary foci of pneumonitis which certainly account in part for the higher temperatures that were observed.

The pulse rate in exposed subjects is increased but usually not in proportion to the increased respiratory rate. Physical examination elicits pulmonary signs that are compatible with pneumonitis or bronchopneumonia. These findings may be confirmed by roentgenography. The physical signs and symptoms resemble those of a viral or influenza pneumonia. Death may occur from the fourth day to three weeks after exposure. Convalescence in those who survive is prolonged and may extend for several months.

The prominent physical and laboratory findings in acute nickel carbonyl poisoning are listed in table III.

**Laboratory Findings**

After acute nickel carbonyl poisoning, the concentrations of nickel in urine and feces are greatly increased above the normal.

The results of three day balance studies in dogs before and after exposure to nickel carbonyl are shown in figure 1. It will be seen that immediately after exposure to nickel carbonyl, exceptionally high amounts of nickel are excreted in the urine. Under normal conditions, approximately 90 percent of ingested nickel is excreted in the stool and 10 percent in the urine. However, when nickel is inhaled, the converse results, i.e., most of the inhaled nickel is

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**TABLE III**

<table>
<thead>
<tr>
<th>Findings in Acute Nickel Carbonyl Poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical:</strong> Tachypnea, tachycardia</td>
</tr>
<tr>
<td>Pneumonitis – pneumonia (x-ray)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Cyanosis</td>
</tr>
<tr>
<td>Hepatomegaly – occ.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory: Increased Ni in urine and blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum aminotransferases</td>
</tr>
<tr>
<td>Aspartate (SGOT) &gt;</td>
</tr>
<tr>
<td>Alanine (SGPT) &gt;</td>
</tr>
<tr>
<td>Leukocytes – usually &lt; 12,000 cmm</td>
</tr>
<tr>
<td>Arterial pO2 – decreased</td>
</tr>
<tr>
<td>Serum Na and Cl &lt;</td>
</tr>
<tr>
<td>Serum K &gt;</td>
</tr>
<tr>
<td>Hyperglycemia and glucosuria – occ.</td>
</tr>
</tbody>
</table>
excreted in the urine and only a relatively small percentage is excreted in the stool.\textsuperscript{52,53} The observation that there is a sharp increase in the nickel excretion in the urine immediately after exposure to nickel carbonyl has proved to be of major practical value and has led to the development of procedures for detecting accidental exposure to minimal amounts of nickel carbonyl in concentrations too low to produce immediate symptoms.

In humans, the concentrations of nickel in urine may remain increased for ten or more days after exposure. However, exceptions occur and have been found in our most critically ill patients,—one of whom died. It is suspected that this may be related to the nephritis that may develop.

The serum aminotransferases are usually increased after exposure (table III). The aspartate transferase (SGOT) level is increased in about one-third of the patients during the first few days, reaching a peak on the seventh day. The alanine transferase (SGPT) level is apt to increase more rapidly, and the higher values persist longer than those for SGOT.\textsuperscript{56}

The leukocyte count seldom rises higher than 12,000 per cmm. Alterations in the serum electrolytes occur in patients and in experimental animals exposed to nickel carbonyl.\textsuperscript{45} These alterations follow the pattern encountered during the precritical period of pneumonia.\textsuperscript{38} They include diminished concentrations of serum sodium and chloride associated with increased concentrations of potassium. Such metabolic changes are also compatible with the findings observed in acute adrenal cortical insufficiency.\textsuperscript{57} The favorable response of patients to corticosteroid therapy as an adjunct to Dithiocarb administration is consistent with the observed electrolyte changes.

Vuopala\textsuperscript{56} obtained pulmonary function tests in 25 patients suffering from acute nickel carbonyl poisoning. Although his results are not entirely uniform, they are nevertheless consistent with those obtained with acute interstitial lung disease.

**Nickel in Tissues**

The concentrations of nickel in lung and liver tissues obtained at necropsy after acute nickel carbonyl poisoning are increased, as shown in table IV.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lung (µg Ni/100 g wet weight)</th>
<th>Liver (µg Ni/100 g dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stab wound</td>
<td>2.40</td>
<td>14.6</td>
</tr>
<tr>
<td>Drug intoxication</td>
<td>2.20</td>
<td>12.1</td>
</tr>
<tr>
<td>Hanging</td>
<td>0.81</td>
<td>3.3</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>0.96</td>
<td>4.3</td>
</tr>
<tr>
<td>Mean</td>
<td>1.59</td>
<td>8.6</td>
</tr>
<tr>
<td>Acute nickel carbonyl</td>
<td>17.3</td>
<td>115.0</td>
</tr>
<tr>
<td>poisoning</td>
<td>5.3</td>
<td>20.7</td>
</tr>
</tbody>
</table>

![Figure 1: Nickel balance studies in dogs before and after exposure to nickel carbonyl.](image-url)
trations of nickel in the lung and liver tissues are, respectively, 11 and 6 times greater than the average concentrations of nickel found in the lung and liver control tissues obtained from persons dying from stab wounds, drug intoxication, hanging and carbon monoxide poisoning.39

Pathologic Findings

The most significant pathologic changes in acute nickel carbonyl poisoning are found in the lungs. The lesions in fatal cases of acute nickel carbonyl poisoning have been summarized in the recent monograph on nickel.17 The lungs of animals that die soon after exposure show a severe degree of congestion and pulmonary edema whereas the animals surviving one to five days usually show extensive pneumonitis.40 Most prominent among the histopathologic findings in man are hyaline membrane formation, edema and dilatation of the alveolar capillaries secondary to congestion. The alveolar lining cells in most areas display degenerative changes. The histologic findings in the liver reveal congestion of central and portal vein branches with slight central hepatic degeneration. Sections of the kidneys and brain frequently reveal congestive changes.

The histopathologic findings in the lung tissue with Legionnaires’ Disease are practically the same as those observed in patients who died from acute nickel carbonyl poisoning.

Microscopic sections of lung tissues from acute nickel carbonyl poisoning and from Legionnaires’ Disease are shown in figures 2 and 3, respectively. The histologic features in both conditions are those of an acute interstitial pneumonitis displaying mainly degenerative rather than reactive or regenerative changes, such as are observed in pneumonitis of infectious origin.

Antidote for Acute Nickel Carbonyl Poisoning

In 1958, our laboratory discovered that sodium diethyldithiocarbamate (Dithiocarb) was dramatically effective in counteracting the lethal effects of nickel carbonyl inhalation in experimental animals.34,47,54 This led us to employ the chemical in humans who had been accidentally exposed to nickel carbonyl. These exposures occurred in conjunction with a variety of industrial uses of nickel carbonyl. To date, more than 350 workmen, accidentally exposed to nickel carbonyl, have received Dithiocarb. To the best of our knowledge, no exposed workman died who received Dithiocarb within the first five days after exposure.

The observation of a sharp increase in the nickel excretion in the urine immediately after exposure, even before the onset of symptoms,53 has led to the development of procedures whereby certain manufacturing plants using nickel carbonyl in their operations measure the concentration of nickel in the urine of workmen at the end of each working shift. In those instances in which increased concentrations of nickel in urine above 10 micrograms per 100 milliliters of urine are reported, the workmen are given Dithiocarb as a preventive measure even though they may have developed no symptoms of exposure or may not have been aware that they had ever been exposed to nickel carbonyl. Such preventive measures have proven to be exceptionally effective in reducing the hazards of exposure.39

An industrial accident occurred within recent years in which four men were exposed to high concentrations of nickel carbonyl vapor. Three of the men received Dithiocarb through their industrial dispensary 24 hours after exposure, but the fourth man was hospitalized by his family physician and treated for
Figure 2. Microscopic view of lung tissue in a patient with fatal acute nickel carbonyl poisoning. The alveolus is filled with edema fluid. The alveolar wall is lined by hyaline membrane. An infiltrate composed mainly of round cells and polymorphonuclear leukocytes is present in alveolar tissue. H & E stain × 500.

Figure 3. Microscopic view of lung tissue in a patient with fatal Legionnaires' Disease. The histologic features are similar to those shown in figure 2: H & E stain × 550.
bronchopneumonia with antimicrobial drugs without benefit of Dithiocarb. The three workmen who received Dithiocarb became symptomless and returned to work within 72 hours after exposure. The fourth man who had not received Dithiocarb died within six days after exposure. The concentrations of nickel in the urine samples obtained from all four workmen were elevated. The concentrations of nickel in the lung and liver tissues obtained at autopsy from the workman who died after exposure to nickel carbonyl were increased several fold, as shown in table IV. The history, physical and laboratory findings left no doubt that the hospitalized, exposed workman who had not received Dithiocarb died of acute nickel carbonyl poisoning. In retrospect, this accident not only illustrates the therapeutic effectiveness of Dithiocarb in treating nickel carbonyl poisoning, but also emphasizes the fact that the diagnosis of acute nickel carbonyl poisoning may be readily overlooked in customary hospital practice.

Although supplies of Dithiocarb were made available for the hospitalized patients suffering from Legionnaires' Disease, none of the patients received this medication.

**Estimate of the Quantity of Nickel Carbonyl That Might Be Lethal to 16 Percent of Exposed Persons**

The question has been raised as to the amount of nickel carbonyl capable of causing 29 deaths in 177 sick persons. This amount can be estimated by making the reasonable assumptions given in table V.

From our previous studies on the mortality rates of rats exposed to various concentrations of nickel carbonyl for 30 minutes, it is possible by probit analysis to calculate the concentration of nickel carbonyl in air that will yield a mortality rate of 16 percent. The LD₁₆ for rats is calculated to be 0.08 milligram of nickel carbonyl per liter of air for an exposure period of 30 minutes.

To fill a room of 12,500 cubic feet (353,750 liters) with nickel carbonyl to a concentration of 0.08 milligram per liter would require 28.3 grams of nickel carbonyl. If allowance is made for ventilation at a turn-over rate of three times per hour, the amount of nickel carbonyl for an exposure period of 30 minutes would amount to 42.5 grams. The density of nickel carbonyl is 1.32. Therefore, this would amount to 32.2 milliliters or a little more than a fluid ounce.

Since the vapor of nickel carbonyl has 5.9 times the density of air, the vapor would tend to be more concentrated at the lower levels of any space. Therefore,

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*The Legionnaires used 13 hotel hospitality rooms where they brought in their own food and beverages. No records were kept of the attendance in these rooms; however, it appears that one room was implicated more than the others. It is noteworthy that hotel employees were not present in the hospitality rooms since there was no need for their services. If exposure to the toxic agent occurred in one of the hospitality rooms, this may account for the fact that none of the hotel employees became ill.*

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**TABLE V**

Estimate of Amount of Nickel Carbonyl Lethal for 16 Percent of Exposed Persons

<table>
<thead>
<tr>
<th>ASSUMPTIONS</th>
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<tbody>
<tr>
<td>1. Exposure was made in a room 50 x 20 x 12.5 feet. Volume = 12,500 cubic feet or 353,750 liters.</td>
</tr>
<tr>
<td>2. Turnover of air in room was once every 20 min.</td>
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<tr>
<td>3. Sixteen percent (29 out of 177) of exposed persons died.</td>
</tr>
</tbody>
</table>

**EXPERIMENTALLY DERIVED DATA**

LD₁₆ for rats = 0.08 mg per liter of air for 30 min.

Amount of Ni(CO)₄ required:

\[
\frac{353,750 \times 0.08}{1,000} \times \frac{20}{20} = 42.5 \text{ g}
\]

[Sp. Gr. of Ni(CO)₄ is 1.32]

- 32.2 ml
- 1.1 fl oz

Allowing 7.5 fold margin for uncertainty, one half pint of Ni(CO)₄ should suffice.
it can be estimated that in the assumed room of 12,500 cubic feet, a fluid ounce of nickel carbonyl would be at least lethal within five days for 16 percent of rats exposed for 30 minutes.

If a half pint of nickel carbonyl were vaporized in the same sized room, this would provide a 7.5 fold factor for uncertainty. Therefore, it would seem to be a reasonable estimate that a one half pint flask filled with nickel carbonyl and vaporized for 30 minutes in a room of 12,500 cubic feet would be more than necessary to produce 16 percent of deaths in exposed persons. It has been speculated that the legionnaires might have been victims of sabotage. Considering the relative ease with which nickel carbonyl might be procured, its use for purposes of sabotage should be investigated. At the congressional hearings, it was reported that persons hostile to legionnaires moved around the hotel making statements that “Legionnaires are doomed.”

In retrospect, it would be relatively easy for a saboteur to spill nickel carbonyl, which has the appearance of vodka or gin, on the carpet or a tablecloth without attracting much attention. In such an event, the nickel carbonyl would evaporate rapidly without leaving a detectable odor or noticeable trace.

Nickel Carbonyl as a Carcinogen

The high incidence of pulmonary cancer in nickel workers was first reported in 1937. Since that time, the relation of the inhalation of nickel carbonyl to pulmonary carcinogenesis has been the subject of numerous investigations. In 1958, it was shown in Wales that 35.5 percent of nickel workers died of cancer of the lung or upper respiratory tract whereas the incidence among the coal miners in the same area was only 1.5 percent. The average age at death in the nickel workers was 57.6 years. The average length of time that affected workers were employed in the nickel refineries was 27 years; the average time between the first exposure and death from lung cancer was 30.5 years.

In our studies on nickel carcinogenesis, pulmonary cancers were induced in rats by two methods of exposure to nickel carbonyl: (1) a single, heavy exposure to a concentration of 250 micrograms of nickel carbonyl per liter of air for 30 minutes and (2) multiple exposures to a concentration of 30 micrograms of nickel carbonyl per liter of air for 30 minutes, three times weekly, for one year. It is noteworthy that pulmonary cancers in our rats were not observed until two years or more after the initial exposure. It might also be emphasized that the induction of pulmonary cancer in a laboratory rat is a severe challenge, in as much as spontaneous pulmonary neoplasms rarely occur in this animal.

One of our patients, a chemical engineer, survived one severe exposure to nickel carbonyl during the construction of an industrial plant. This exposure occurred before Dithiocarb had been discovered. Consequently, the engineer received no specific antidote. Approximately eight years after this initial severe exposure, our patient developed a fatal pulmonary cancer.

Assuming that Legionnaires’ Disease might have been caused by exposure to nickel carbonyl, the implications of these observations are obvious.

Suggestions for Consideration

Since pulmonary cancer may develop in experimental animals and in man years after a single, heavy exposure to nickel carbonyl, and assuming that Legionnaires’ Disease was caused by exposure to nickel carbonyl, it is recommended that survivors of Legionnaires’ Disease be given thorough physical examinations.
and chest X-rays annually during the next ten or more years. They should also be given an opportunity to participate in a program of pulmonary, cardiac, hepatic and renal function tests in order to ascertain the long-range sequelae of their exposure. These studies would be helpful aids in the early recognition of neoplastic lesions should they develop.

It is strongly recommended that the survivors of Legionnaires’ Disease be advised to refrain from smoking.

Recognizing the relative ease by which nickel carbonyl can be procured, regulations for its procurement and use should be developed as a safeguard against sabotage and for the protection of the public.

One of the breaches in the investigations of Legionnaires’ Disease was the failure to consider and to include toxicologic examinations in the early phases of the inquiry. Biologic materials should have been collected and saved for toxicologic analyses at the onset of the illness. Any public health team investigating an epidemic should include persons with expertise in clinical toxicology.

Public health authorities should alert practicing physicians that an illness suspected of being a viral or influenzal pneumonia might be actually caused by exposure to a toxic inhalent, particularly nickel carbonyl.

Finally, it is recommended that any patient suspected of suffering from acute nickel carbonyl poisoning receive the specific antidote, sodium diethyldithiocarbamate.

References

22. Foreman, L.: Disease fatal to 29 also killed the Bellevue. Philadelphia Inquirer, November 11, 1976, p. 8-A.


