Therapeutic Properties of Sodium Diethyldithiocarbamate: Its Role as an Inhibitor in the Progression of AIDS*

F. WILLIAM SUNDERMAN Sr., M.D., Ph.D.
Institute for Clinical Science, Pennsylvania Hospital, Philadelphia, PA 19106

ABSTRACT

The therapeutic history of sodium diethyldithiocarbamate (dithiocarb) is briefly reviewed. Dithiocarb was discovered serendipitously in our laboratory 35 years ago for the specific treatment of nickel carbonyl poisoning. Since that time, the therapeutic efficacy of dithiocarb has been reported for many disorders, including: nickel, cadmium, thallium, copper, and mercury poisonings, experimental nickel carcinogenesis, protection against radiation damage to bone marrow, treatment of candidiasis in experimental animals, hepatolenticular degeneration (Wilson’s disease), systemic lupus erythematosis, and human immunodeficiency virus infection (HIV). It has been used as an antagonist to cisplatin and cyclophosphamide toxicities, and as an antidote to hepatotoxicity induced by chloroform, carbon tetrachloride, and halothane.

Most recently, it has been observed that the progression of HIV-1 infection is inhibited by dithiocarb* administered intravenously or orally to patients with acquired immunodeficiency syndrome (AIDS). Attention is directed to the interactions of divalent cations to viral infections and to metal chelators (e.g., dithiocarb) as potential antiviral agents.

Historical

The development of sodium diethyldithiocarbamate as a therapeutic agent began about 35 years ago in our laboratory when our research interests were, to a large extent, concerned with the hazards of exposure to nickel and particularly to nickel carbonyl. During World War II, it became apparent that exposure to nickel carbonyl, an extremely poisonous gas*, presented a serious health hazard and a deterrent to

* At that time, the maximal allowable concentration of nickel carbonyl was set at one part per million in air by the American Conference of Governmental
DITHIOCARB AS AN INHIBITOR IN THE PROGRESSION OF AIDS

Research in atomic energy and to its application in industry. The industrial applications included (1) the separation of nickel from its ores; (2) the preparation of intermediates in organic syntheses; (3) electroplating operations; and (4) as a catalyst for the manufacture of acrylic plastics.

In the early 1950s, our attention was attracted to the metabolic studies of Domar, Fredga, and Linderholm who reported diethyldithiocarbamate to be a metabolic reduction product of disulfiram (antabuse). These studies were of special interest since sodium diethyldithiocarbamate was the chemical used as the nickel binding reagent in our laboratory for measuring nickel in urine by a modification of the Alexander, Godar, and Lindl procedure. Dithiocarb is partially excreted unchanged in urine and bile and a portion undergoes oxidation to form free and ethereal sulfates as well as metal complexes. The structure of the nickel chelate of diethyldithiocarbamate was studied by Vaciago and Fasana and is portrayed in figure 1. Excluding for the ethyl groups, the nickel in the complex is a square coplanar hybrid.

In the course of our studies, it was discovered that soluble salts of various specific dithiocarbamic acid derivatives exerted a remarkable detoxifying effect against active nickel compounds which had been absorbed, ingested, inhaled, or otherwise taken up by warm blooded animals. Of 13 soluble salts of dialkyl-dithiocarbamic acid tested (table I), sodium diethylthiocarbamate (dithiocarb) proved to be among the least toxic and one of the most effective. The LD₅₀ value for the sodium salt administered to mice and rats was 1.5 gram per kilogram of body weight.

Sodium diethylthiocarbamate is a chelating agent which forms metallic complexes with a number of metallic ions. Gale, Smith, and Walker prepared buffered aqueous solutions of 14 metal compounds and to each of them they added an equal volume of an unbuffered solution of dithiocarb. Heavy flocculent precipitates formed with the following metallic salt solutions: Ag⁺⁺, Cd⁺⁺, Co⁺⁺, Cu⁺⁺, Fe⁺⁺⁺, F⁺⁺⁺, Hg⁺⁺, Mn⁺⁺, Ni⁺⁺, Pb⁺⁺, Sn⁺⁺, and Zn⁺⁺. Of the divalent cations tested, it is noteworthy that solutions of Ca⁺⁺ and Mg⁺⁺ do not form precipitates with dithiocarb. Studies with ultra violet absorption spectrum gave reasonably conclusive evidence that Ca⁺⁺ and Mg⁺⁺, biologically essential ions, produced no binding with dithiocarb.

Since it was deemed essential to determine whether or not calcium and magnesium were affected by the administration of dithiocarb in vivo, measurements were made of the concentrations of serum calcium and magnesium in dogs receiving dithiocarb in doses of 30, 100, and 300 mg per kg of body weight for a period of 90 days. The measurements were all within the normal limits. Furthermore, histopathologic studies of the bones failed to reveal any mobilization of calcium.

Since dithiocarb binds trivalent iron in vitro, it might be expected to interfere with hematopoiesis by binding iron either in the gastrointestinal tract or in the serum. Sunderman, Paynter, and George measured the concentrations of hemoglobin, the mean hematocrit values, and the erythrocyte counts at 30 and 90 day intervals in a control group of rats and a group receiving dithiocarb at
Sodium diethyldithiocarbamate + Ni$^{2+}$ → Nickel bis(diethyldithiocarbamate)

**Figure 1.** Chelation of nickel by Dithiocarb.

The level of 300 mg per kg of body weight. At the 30 day interval, no significant differences were observed in the hematologic values between the control and test groups. However, at the 90 day interval, both the male and female test groups had significantly decreased mean erythrocyte counts. The mean concentrations of hemoglobin and the hematocrit values for the female test group were also significantly lower than those of the female control group. Similar measurement of iron were made in dogs receiving dithiocarb in high test doses of 300 mg per kg per day at intervals of 45 and 90 days. These studies showed a consistently downward trend in the initial values when compared with the control group.

Studies were then undertaken to determine the effectiveness of dithiocarb administered to experimental animals acutely exposed to nickel carbonyl. The dramatic effectiveness of dithiocarb in counteracting the lethal effects of nickel carbonyl in experimental animals led us to administer this chemical to humans who had been accidentally exposed to nickel carbonyl.

After having served as the first control subject by taking a dose of dithiocarb without ill effects, dithiocarb was administered therapeutically for the first time to a workman who had been severely exposed to nickel carbonyl through accidental spraying. After resuscitation, this patient was given dithiocarb orally and became entirely symptom-free on the second day of hospitalization, although the concentration of nickel in his urine did not reach normal levels until 16 days after exposure. The dramatic effectiveness of dithiocarb in the treatment of nickel carbonyl poisoning in this patient initiated its expanded therapeutic use during the ensuing years.

**Therapeutic Uses of Dithiocarb**

Many studies on the chemotherapeutic properties of dithiocarb and the effects of its prolonged administration have been published.

<table>
<thead>
<tr>
<th>Therapeutic Use of Sodium Diethyldithiocarbamate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chelating agent in metal poisonings: Ni, Cd, Th, Cu, Zn, Hg, Co, Pb</td>
</tr>
<tr>
<td>2. Inhibitor in the progression of AIDS and ARC</td>
</tr>
<tr>
<td>3. Treatment for specific disorders:</td>
</tr>
<tr>
<td>A. Hepatolenticular degeneration</td>
</tr>
<tr>
<td>B. Systemic lupus erythematosis</td>
</tr>
<tr>
<td>C. T-cell deficiency</td>
</tr>
<tr>
<td>4. Antidote for poisoning from polyhalogen compounds: CHCl₃, CCl₄, and C₂BrClF₃ (halothane)</td>
</tr>
<tr>
<td>5. Miscellaneous group</td>
</tr>
<tr>
<td>A. Tumors and as an adjunct in cisplatin therapy</td>
</tr>
<tr>
<td>B. Protection against radiation sensitization</td>
</tr>
<tr>
<td>C. Inhibition of fungal infections (Candidiasis)</td>
</tr>
</tbody>
</table>

AIDS = acquired immunodeficiency syndrome  
ARC = AIDS related complex
Although most of the studies in past years pertain to dithiocarb’s remarkable antidotal properties in nickel poisoning, nevertheless, more recently its therapeutic effectiveness in other disabilities have been reported and, in particular, its usefulness as an inhibitor to the progression of acquired immunedeficiency syndrome (AIDS).

A listing of the early therapeutic uses of dithiocarb as a chelating agent in nickel, copper, thallium, and polonium poisoning was reported in 1967.74

The therapeutic efficacies of dithiocarb for various disorders are outlined in table I.

**Chelating Agent in Metal Poisonings**

Any consideration of treatment in poisons requires a knowledge of the physical and chemical characteristics of the substance to which the subject has been exposed, the concentration, the length and type of exposure as well as the sensitivity of the host, idiosyncracies, and presence of disease.

**Nickel**

During the past 30 years, more than 400 persons exposed to the inhalations of nickel carbonyl have been treated under our supervision with dithiocarb.56,58,61,63,64,68,71,73,86 To our knowledge, no death from acute nickel carbonyl poisoning occurred in any person who received adequate dithiocarb medication within two to three days after exposure. A comprehensive review of the use of dithiocarb in the treatment of nickel carbonyl poisoning has recently been published.54 It might be mentioned that death from acute nickel carbonyl poisonings usually occurs within five to 12 days after exposure. The types of nickel poisoning that may be encountered are listed in table II.56

### Types of Nickel Poisoning

<table>
<thead>
<tr>
<th>Inhalation (Ni(CO)4, Ni, Ni3S2, NiO, Ni2O3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
</tr>
<tr>
<td>Pneumonitis with adrenal cortical insufficiency; hyaline membrane formation; pulmonary edema and hemorrhage; hepatic degeneration; brain and renal congestion</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
</tr>
<tr>
<td>Cancer of respiratory tract; pulmonary eosinophilia (Loeffler’s syndrome); asthma</td>
</tr>
<tr>
<td><strong>Skin Contact</strong></td>
</tr>
<tr>
<td>Primary irritant dermatitis; allergic dermatitis; eczema</td>
</tr>
<tr>
<td><strong>Parenteral (Prosthetic Implantations)</strong></td>
</tr>
<tr>
<td>Allergic reactions; osteomyelitis; osteonecrosis, malignant tumors</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
</tr>
<tr>
<td>Gastroenteritis; nausea; vomiting; abdominal pain; myalgia</td>
</tr>
</tbody>
</table>

The treatments of nickel poisoning from inhalation and skin contact have been the most extensively studied.

The carcinogenicity of nickel and certain of its diverse compounds has been the subject of many studies and a number of reviews.12,20,21,31,34–36,42,60,63–66,69,70,72,75–83

During the past several years, the antitumorigenic effectiveness of dithiocarb on nickel induced tumors has been investigated in our laboratory.54,56,63,69,70 Originally, it had been inferred that nickel carbonyl was the most carcinogenic of inhaled nickel compounds; however, investigations by Gilman and Ruckerbauer,19 and Gilman18 revealed that nickel subsulfide (Ni3S2) was the most carcinogenic component of metallurgical dust obtained from refinery flue stacks. As a result, studies were undertaken to ascertain the possible effectiveness of dithiocarb on the development of tumors in rats following muscular implantations of nickel subsulfide.54,55,67

Our studies69 showed that 78 percent of untreated rats develop sarcomas after implantations of nickel subsulfide, whereas in rats that were treated with
dithiocarb for a period of four to six weeks after implantation, only 32 percent developed sarcomas. Analyses of the data revealed a striking difference in the sex responsiveness to dithiocarb. Of the 25 female rats with Ni$_3$S$_2$ implants and treated with dithiocarb, only 12 percent (three rats) developed sarcomas; of the male rats similarly treated, 52 percent (13 rats) developed sarcomas. The difference in sex response is statistically significant (p = 0.005).

Cadmium

Gale Smith, and Walker$^{17}$ studied the protective effect of dithiocarb on cadmium poisoned mice. They found that dithiocarb protected mice from lethal doses of CdCl$_2$. More than 98 percent of the mice receiving 500 mg of dithiocarb per kg of body weight survived if treated within five hours after CdCl$_2$ administration. These investigators postulated that dithiocarb is an effective modular of acute cadmium toxicity. Jones and coworkers$^{24}$ reported that dithiocarb administered to cadmium poisoned mice yielded higher survival rates and less cadmium retention in the brain, liver, and kidney than other chelating agents tested. Reports of the protective effect of dithiocarb in cadmium poisoning appear to be limited to studies in experimental animals.$^{13,15,16,17,24,41}$

Copper

Bizzi, Garattini, and Mor$^3$ observed that dithiocarb was an effective antidote to copper chloride poisoning in rats. After the daily ingestion of dithiocarb in dogs in doses of 30, 100, and 300 mg per kg of body weight, Sunderman, Paynter, and George$^{68}$ measured the concentrations of serum copper at intervals of 21 and 90 days. The mean values for the analyses in the control and the test groups are plotted in figure 2. It will be seen that the increased concentrations were correlated with the dosage of dithiocarb. Although copper balance studies were not undertaken, it seems reasonable to assume that the increased concentrations of copper in serum are a reflection of the degree of chelation and the increased concentrations of copper in the urine. (See comments under Hepatolenticular Degeneration.)

Zinc

Although dithiocarb chelates zinc ions, its administration did not affect the histologic pancreatic structure or the serum glucose concentrations in rabbits.$^{29,38}$ Furthermore, our studies on dogs$^{68}$ did not support the view that dithiocarb might lead to the disappearance of alpha cells of pancreatic islets and that it might be attended by visual disturbances.$^{25}$ Our studies failed to reveal any histopathologic changes in pancreatic tissue or any effect on the concentrations of serum glucose in test animals receiving dithiocarb for periods of 90 days. Moreover, no impairment of vision nor alterations in the structure of the eyes were observed in any of our experimental animals.
Lead, Mercury, Cobalt, and Polonium

Gale and coworkers evaluated the effectiveness of dithiocarb in mice that had been given lead acetate. They found that dithiocarb given orally was effective in reducing the whole body burden of lead but that it caused a substantial increase in the levels of lead in the brain.14

Dithiocarb was found to be only partially effective in the treatment of mercury vapor poisoning.57 In so far as was ascertained, no studies on the effects of dithiocarb on silver, cobalt, or manganese intoxications in either experimental animals or humans have been made.

Krivchenkova and Safronov reported that dithiocarb mobilized polonium in rats and dogs.26a

Thallium

Two patients suffering from thallotoxicosis were reported to have obtained excellent beneficial clinical response following intravenous and oral administration, respectively, of dithiocarb.2,74 Stavinoha, Emerson, and Nash51 reported that dithiocarb was effective against thallium poisoning in mice, and Schwetz and coworkers50 observed that the compound increased the urinary excretion of radioactive thallium nitrate administered to rats. In a review of thallium poisoning, Saddique and Peterson48 point out that although the intravenous administration of dithiocarb increases the urinary excretion of thallium significantly; nevertheless, these increases are attended by clinical deterioration in the level of consciousness and in electroencephalographic disturbances.

AIDS and ARC

Inhibition to the Progression of AIDS

Pompidou and coworkers44 presented a preliminary report in 1985 on the therapeutic effectiveness of dithiocarb in three patients with acquired immunodeficiency syndrome related complex (ARC). They conceived the idea of studying the effect of immunomodulators that increased the percentage and absolute numbers of T-cells. Isoprinosine and dithiocarb were the immunomodulators that were selected. These workers found that dithiocarb administered to three ARC patients showed a short term improvement without any side effects.

Lang et al27 also reported in 1985 that they had given dithiocarb orally to six previously untreated male homosexuals with ARC in dosages of 8 to 10 mg per kg of body weight once a week for three to six months. They noted slow clinical improvement in all of the patients in the absence of any decrease in the number of T4 cells. In 1988, Lang and 13 coworkers28 published a randomized double-blind placebo-controlled trial of dithiocarb in 83 patients with HIV infection over a period of 16 weeks. The infection did not progress in the dithiocarb-treated group but did so in four patients in the placebo group. These investigators noted that the dithiocarb-treated group was associated to a greater extent than the placebo group "with relief of constitutional symptoms, improvement in clinical status (including shrinkage of enlarged spleen and lymph nodes), and improvement in immune function (as measured by CD4+ cell count and skin test reactivity)."

Two important investigations have been reported within the past year on the therapeutic effects of dithiocarb in the treatment of AIDS and AIDS-related complex (ARC).4,45

In a pilot study undertaken by Brewton and five coworkers,4 40 randomized patients received either dithiocarb 200 mg per m^2 intravenously weekly for 16 weeks or no therapy. These workers reported a significant decrease in the symptoms in the dithiocarb-treated patients as compared to the controls (P = 0.002). They observed a significant
improvement in lymphadenopathy in the treated patients compared to the controls ($P = 0.005$); however, they noted no significant differences in the progression of the disease.

The important study by a group headed by Reisinger has been released this year indicating the inhibition of HIV progression by dithiocarb. Sixty patients with HIV infection (in Walter Reed Stages 2 to 4) were randomized to treatment with intravenous or oral dithiocarb or with a placebo for 24 weeks in a paired double-blind investigation. An evaluation of 55 patients at the end of the study noted that no patient who had received dithiocarb had AIDS, whereas six placebo patients did. A significantly delayed progression of the disease was observed in the group receiving dithiocarb intravenously compared to the matching placebo group. A follow-up study of 21 patients in the dithiocarb group and 26 patients in the placebo group was made 18 months after the study had begun. It was revealed that in the original placebo group three patients had died, eight patients had AIDS, and 18 patients had progressed into CDC staging. In the original dithiocarb group, no patient had died, two had AIDS, and nine had progressed in CDC staging. This noteworthy study revealed significant differences in the progression of AIDS and CDC staging between the dithiocarb and placebo group ($P < 0.05$).

Discussion

Many studies have called attention to the concept of using metal chelating agents in the chemotherapy of viral infections. The literature pertaining to this subject has been thoroughly reviewed by Levinson, Perrin and Stunzi, Hutchinson, and Williams. The antiviral potentials of dithiocarb as an inhibitor of the progression of AIDS appear to be well established. As a chelator of divalent cations, dithiocarb inhibits the action of metallic dependent enzymes, notably copper and zinc, and it seems reasonable, therefore, to suggest that dithiocarb has a chelating effect on the enzymatic pathways that may be required for HIV infection.

At the recent Sixth International Conference on AIDS, held in San Francisco, it was repeatedly postulated that "there are shortcomings to the idea that HIV alone causes all the symptoms of the disease or the rate of progress to an AIDS-defining condition." The existence of a cofactor was postulated by several participants, i.e., "a mycoplasma that somehow enters the infected cell and not only directly causes many of the ills that afflict people with HIV infection, but that increases viral replication and thus ultimately kills the infected person." It is obvious that if the cofactor could be contained, effective therapy should be established.

The question thus may be raised, could the cofactor in the activation of HIV be a metal-dependent enzyme? If so, this might explain the inhibitory effect of dithiocarb on the progression of AIDS through chelation of the metal contained in the activating enzyme.

Treatment of Specific Disorders

Dithiocarb has been alleged to be therapeutically effective in several specific disorders, two of which may be briefly cited.

Hepatolenticular Degeneration (Wilson's Disease)

Sunderman, White, and Sunderman reported their studies on a 34-year-old woman with Wilson's disease that were undertaken over a five month period. Dithiocarb was administered to the patient both orally and intravenously. Daily intravenous administrations in
doses of 10 to 20 mg per kg of body weight resulted in increased urinary excretions of both copper and nickel. These increases were attended by a distinct clinical improvement, – the tremor diminished, the speech became less slurred, and the patient was able to assist in feeding herself. It was remarkable that redness of the conjunctivas in the proximity to the Kayser-Fleischer rings developed within five minutes after the intravenous injections were started.

This conjunctival irritation was associated with a local burning sensation and mild lacrimation which persisted for approximately 15 minutes following the termination of the injections. It is believed that the rapidity of the conjunctival reaction may denote a selective localization of dithiocarb in the Kayser-Fleischer rings. After continued dithiocarb therapy, the patient became able to speak clearly and to return to light housework. The Kayser-Fleischer corneal rings became less prominent, and measurements of hepatic function returned to the normal ranges. After two years of treatment and observation, the Kayser-Fleischer rings practically disappeared, and the patient remained in reasonably good physical condition. This therapeutic response is noteworthy since the typical patient with Wilson’s disease follows a course of unremitting severity and fatal outcome.

**Systemic Lupus Erythematosus (SLE)**

Delepine and coworkers reported that dithiocarb induced a long-lasting remission in a 14-year-old girl suffering from SLE. Within eight weeks after the administration of dithiocarb and after prednisone therapy had been reduced, the patient achieved a complete remission. One year after starting treatment with dithiocarb and more than six months after prednisone had been stopped, the patient was well, and the hematological values had returned to the normal ranges.

**T-cell Deficiencies**

In a study of the clinical characteristics of dithiocarb, Lemarie et al reported that this agent was therapeutically effective in syndromes in which the underlying defect was T-cell deficiency or dysfunction. These clinical disabilities included tuberculosis, chronic bronchitis, bronchiectasis; and chronic infections and rheumatoid arthritis in the elderly. In experimentally induced pleurisy with calcium pyrophosphate, dithiocarb partially restored the inflammatory responses and other immune parameters.

**Antidote for Poisoning from Polyhalogen Compounds**

The antidotal effects of dithiocarb against carbon tetrachloride-induced hepatotoxicity were first described by Sakaguchi et al. Siegers and coworkers found that dithiocarb afforded a nearly complete protection against liver damage in mice induced by the oral administration of carbon tetrachloride, allyl alcohol, bromobenzene, and thioacetamide, respectively. Eade et al suggested that dithiocarb protection against halothane-induced liver damage in rats was presumably due to its action as a scavenger of free radicals formed during the metabolism of halothane.

**Other Therapeutic Considerations**

Recent studies have revealed that the therapeutic efficacy of cisplatin in the treatment of malignant murine tumors may be enhanced by dithiocarb. Murthy et al have demonstrated that by combining cisplatin with dithiocarb, high doses of cisplatin can be safely adminis-
tered. When localized hyperthermia is combined with high doses of cisplatin and dithiocarb, the retardation of tumor growth and the prolongation of host survival are significantly better than those obtained with the highest tolerated dose of cisplatin alone or cisplatin plus hyperthermia.

The protection of mammalian cells from radiation by dithiocarb has been shown by several in vivo and in vitro studies. Dithiocarb is reported to be both fungicidal and insecticidal. Walker and his group evaluated the dithiocarbamates as antifungal agents in mice. They concluded that the combination of dithiocarb and amphotericin-B was effective treatment for systemic Candidiasis infections.

Summary

The efficacy of sodium diethyldithiocarbamate for the treatment of many disorders has been briefly reviewed. Of particular interest are the recent studies of dithiocarb as an inhibitor in the progression of AIDS.

References

DITHIOCARB AS AN INHIBITOR IN THE PROGRESSION OF AIDS


47. RENOUX, G.: (Int.) Symposium on New Trends in Human Immunology and Cancer. Immuno-
SUNDERMAN SR.


