American Industrial Hygiene Association Journal

ISSN: 0002-8894 (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/aiha20

Prophylactic chelation therapy in occupational lead poisoning: a review

KENNETH BRIDBORD & HECTOR P. BLEJER

To cite this article: KENNETH BRIDBORD & HECTOR P. BLEJER (1977) Prophylactic chelation therapy in occupational lead poisoning: a review, American Industrial Hygiene Association Journal, 38:10, 536-542, DOI: 10.1080/0002889778507667

To link to this article: https://doi.org/10.1080/0002889778507667

Published online: 04 Jun 2010.

Chelating agents are useful in the therapy of acute overexposure to lead. However, prophylactic use of chelating agents, particularly under conditions of continued exposure to lead can be harmful to health. Potential adverse effects include kidney damage, symptomatic lead poisoning, increased absorption of lead from the gastrointestinal tract and disruption in the metabolism of trace metals other than lead. Prophylactic chelation is an unacceptable medical practice which cannot be condoned.

Prophylactic chelation therapy in occupational lead poisoning: a review

KENNETH BRIDBORD, M.D. and HECTOR P. BLEJER, M.D., D.I.H.
National Institute for Occupational Safety and Health, 4500 Fishers Lane, Rockville, Maryland 20857; City of Hope Medical Center, 1500 E. Durante Road, Durante, California 91010

introduction

Recently it has become necessary to reassess the proper medical role of the practice of prophylactic chelation therapy in the control of occupational lead poisoning due to reports that such therapy continues to occur in the United States.[1,2]

Prophylactic chelation is herein defined both a) as the routine use of chelating or similarly acting drugs to prevent elevated blood lead levels in workers who are occupationally exposed to lead, or b) as the use of these drugs to routinely lower blood lead levels to predesignated concentrations believed to be "safe". A number of studies have been published on the use of calcium disodium edetate (EDTA, $CaNa_2$, EDTA) a chelating agent, and penicillamine in the therapy of lead intoxication. Most authorities agree that chelating or similarly acting agents have a proper place in the therapy of the acute symptomatology of severe lead intoxication, a condition accompanied by pronounced gastroenteric, neurologic and other symptoms and signs.

The primary focus of this review deals with questions of the health risk involved in chelation therapy and especially the use of prophylactic chelation therapy, particularly under conditions of continued exposure to lead.

review and discussion

effect of chelating agents on excretion of lead from the body and on blood lead levels

A number of studies has examined the effect of chelating agents upon excretion of lead from the body and in most instances increased urinary excretion of lead has been observed. Treatment, however, has not always resulted in lowered blood lead levels.

The oral and intravenous effects of EDTA on urinary lead excretion were examined in 5 adults and 2 children who either had symptoms of lead poisoning or excessive amounts of lead in the blood or urine.[3] Intravenous and oral doses were each accompanied by increased urinary lead excretion compared to pretreatment values.

The use of oral EDTA in the therapy of childhood lead intoxication was examined in subjects with a documented history for lead intoxication.[4] Patients were given oral EDTA at 75 mg/kg/day for a period of nine days. The medication produced increases in urinary lead excretion and decreases in blood lead levels in all patients compared to pretreatment levels.

The oral EDTA effect on lead concentrations in the blood and urine of twelve battery workers was examined.[5] These twelve men were given oral medication for 5 days a week for 2-3 weeks at a dosage of 60 mg/kg/day. After one week of

treatment average blood lead levels dropped by 10 μg/100 ml and, by the end of the third week, blood lead levels dropped by another 10 μg/100 ml. However, 3 subjects showed an elevated blood lead level at the end of the experiment compared to the beginning.

Fecal and urinary lead excretion was evaluated in 3 men with occupational lead poisoning before, during and after treatment with EDTA both orally and intravenously.[6] Subjects were removed from exposure during the course of the study. Combined urine and fecal lead excretions in these men were found to increase by a factor of 2-3 while receiving therapy. Both urinary and fecal lead excretions were increased during oral treatment. However, during intravenous (IV) therapy urinary lead excretion was greatly increased, while fecal lead excretion was diminished.

The treatment of lead poisoning by oral EDTA in 5 adult subjects with industrial lead poisoning was studied.[7] Dosages were given at 4 g/day for several days, followed by a rest period of 7 days and then an additional course of therapy similar to the first. The subjects were removed from hazardous exposure prior to treatment. Oral medication caused a 5- to 20-fold increase in urinary lead excretion which greatly exceeded the quantity of lead in circulating blood prior to treatment, suggesting a mobilization of lead from the bone. Blood lead levels tended to fall immediately following treatment, but in some cases this was followed by a rise in blood lead concentrations. Eight men with excessive lead absorption who were given oral EDTA for periods of 7 days were evaluated.[8] Urinary lead excretions increased to a maximum of 5-11 fold above baseline levels. In 5 patients blood lead levels decreased, in one blood lead remained the same and in one patient blood lead increased following therapy.

effects of chelation therapy on symptoms of lead poisoning

Most studies have demonstrated a beneficial effect of chelation therapy upon acute symptoms of lead intoxication, although in a number of instances symptoms have been observed to occur in workers receiving chelating agents. The literature contains, however, a general dearth of data on long-term follow-up studies of persons treated with chelating agents. For example, one man developed abdominal pain and loose stools following oral medication.[3] Another study evaluated male workers occupationally exposed to lead who were given oral EDTA.[9] Although symptoms were relieved as a result of therapy, symptoms of lead poisoning recurred in about three months after treatment. The investigator warned against giving oral chelating agents under conditions of continued lead exposure. The effectiveness of EDTA therapy in instances of clinical lead poisoning was, however, demonstrated; no significant adverse effects were reported in over 35 patients given oral or IV chelation therapy with EDTA.[9]

In a third study, oral EDTA generally reduced the frequency of lead symptoms such as fatigue, weakness and loss of appetite.[7] In one case, however, headache developed during the first 2 days of therapy. One fatal case was discussed in which the decdent, a woman with lead poisoning, was given IV EDTA treatment which was believed to have accelerated the fatal outcome.

Other authors also reported a beneficial effect of EDTA therapy upon symptoms including constipation, fatigue, poor appetite and difficulty sleeping.[5,8,10]

effects of chelating agents upon the kidneys

A number of laboratory investigations as well as observations in humans has documented the occurrence of kidney damage associated with administration of chelating agents. Investigators studying the renal effects of lead point to the inherent risk of IV EDTA, particularly its potential to induce severe renal damage.[11]

The nephrotoxicity of EDTA was examined in the rat.[12] These studies were prompted by the clinical cases of renal damage following administration of chelating agents, primarily EDTA. Male and female rats were given EDTA intraperitoneally (IP) each day for 10 consecutive days and the animals were sacrificed 24 hours after the last injection. A number of histologic changes was seen in the kidneys of exposed animals. The mildest changes consisted of well demarcated vacuoles in the cytoplasm of the epithelium of the proximal tubule. In the severest cases they progressed to extrusion of cell contents and displacement of cell nuclei.

Vacuolization was not accompanied by increases in serum creatinine or urea nitrogen. Administration of chelating agents to lead poisoned rats, however, did not appear to increase the renal damage which had been caused by the lead. The investigators who conducted that study, however, still considered it prudent to follow renal function closely in patients receiving chelating agents. In this regard, a case of lead poisoning in which renal damage was associated with IV administration of EDTA had been reported.[13]

The effects of lead and of EDTA on the kidneys were evaluated in two recent papers.[14,15] Lead-poisoned rats were given injections of EDTA IP. Inclusion bodies (lead-protein complexes believed to possibly protect against lead effects) in renal cell nuclei were found in various stages of dissolution and migration out of the nucleus. Cytoplasmic vacuoles were observed which contained material that resembled portions of intact nuclear inclusions. Inclusion bodies have not been observed in renal biopsies of male workers occupationally exposed to lead who have been repeatedly treated with chelating agents. Excretion of lead through the kidneys appears to be less in older men compared to younger men who have nuclear inclusion bodies in their renal tubule lining cells. These data suggest that chelation therapy reduces the ability of the kidneys to protect themselves against the toxic effects of lead by virtue of the action of chelating agents in removing the lead-induced inclusion bodies. This conclusion is further supported by observations that renal tubular dysfunction may follow EDTA administration in lead poisoned children.[16]

other effects of chelation therapy

A number of studies suggest that oral EDTA increases the absorption of lead from the gastrointestinal tract in instances where exposure to lead continues to occur.[3,7,9]

Other studies have observed T-wave changes in the electrocardiograms of patients given chelation therapy.[4] Studies also suggest that the metabolism of trace metals other than lead may be affected by long-term chelation therapy.[10,17]

prophylactic chelation programs

Experience during the 1950s in the use of oral $CaNa_2$ EDTA for the prevention of occupational lead poisoning at a battery reclaiming plant has been described.[18] Oral EDTA was given prophylactically 5 days per week for 2 weeks followed by a 2-week rest period, at which time the above dosage scheme was repeated. During the more than one year that this program was in effect, neither cases of acute lead poisoning nor symptoms attributable to lead accumulation in the body were reported among the 16 workers at this plant. It is noteworthy, however, that the hemoglobin level in one of these workers was 11.4 gms; and red blood cell count, 3,880,000, with minimal basophilic stippling present.

previous reviews of chelation therapy

A review of chelation therapy in 1955 warned against the misuse of $CaNa_2$ EDTA for the prophylaxis of lead poisoning.[17] Prophylactic remedies before EDTA became available had been tried with out success, and these were often used in place of the adequate environmental-engineering controls needed to reduce lead exposure in the workplace. That reviewer expressed definite concern that simple and relatively inexpensive medical prophylactic procedures would be favored by management in lieu of expending the necessary funds to obtain safe process design and install proper engineering cntrols. Also, questions were raised as to whether the apparent short-term benefits of chelation therapy outweighed the long-term, potential hazards of its use. In particular, a major concern of that reviewer was that prolonged administration of chelating agents had the potential to disturb the metabolism of minerals in the body. The reviewer concluded that subjecting occupationally lead-exposed workers to prophylactic chelation was "rash and irresponsible".

The treatment of lead absorption in industry was reviewed again in 1958.[19] That author recognized that at high dosages $CaNa_2$ EDTA can cause damage to the kidney. A report of cases was presented of 101 individuals who received oral EDTA at 4 grams per day for 5 days, followed by a rest period of from 5 to 10 days, after which a second course of therapy was given. When used in this manner, the procedure appeared to be reasonably safe. In three workers, however, symptoms were reported

during the course of treatment. The importance of careful monitoring for kidney function was also stressed. Each patient had a urinalysis before the course of treatment and on the third and fifth days during each five-day course of medication. Even at the dosage given, of the 101 workers treated, 9 percent showed albumin or red blood cells in the urine, indicating that some damage to the kidneys perhaps reversible, had occurred. When these urinary effects occurred, the second course of medication was not initiated until the urine had returned to normal, which it did in all instances. However, in 3 cases, the abnormal urinary effects reappeared when the second course of therapy was begun. Among the complaints and effects that were noted in workers taking, and attributed to, this medication were leg cramps, abdominal pain, diarrhea, vomiting, malaise, weakness, constipation, muscle cramps, arthritic pain and pathologic urinary changes. About 30 percent of the individuals taking the drug experienced some adverse symptoms. Nevertheless, the investigator concluded that with oral $CaNa_2$ EDTA treatment individuals could continue working in the lead industry without endangering their health. However, he has also noted that in a few persons exposed to lead and given oral $CaNa_2$ EDTA, renal complications could occur.

The use of EDTA therapy in persons with excessive lead absorption from industrial exposure was reviewed once more in 1959.[20] That author noted that damage to the kidneys has been observed in men given the drug and also in animals when relatively large doses were administered over prolonged periods of time. Moreover, blood lead levels had been observed to rise following intravenous administration of the drug, although without apparent adverse effects. This was usually followed by a decrease in blood lead with urinary excretion of the lead chelate complex, but could also be followed by a rise in blood lead level, as the lead stored in the skeleton was mobilized into the soft tissues. Such effect raised questions of the potential toxic effects to critical organs due to this mobilization of biologically active lead. The author of the 1959 study recommended that persons undergoing chelation therapy should be checked frequently for the possible occurrence of renal damage and did not feel that prophylactic use of EDTA to prevent lead intoxication could be condoned.

Cases of childhood lead poisoning which had been treated with $CaNa_2$ EDTA also were reviewed in 1959.[21] Whereas $CaNa_2$ EDTA is poorly absorbed from the gastrointestinal tract, the lead chelate is rapidly absorbed, suggesting that oral medication should not be given under conditions of continued lead exposure. EDTA is reported to have caused kidney damage in both experimental animals and in man. The reviewer assessed childhood lead poisoning cases all of whom had been treated with IV or intramuscular (IM) injections of EDTA during the acute phase of poisoning. Oral $CaNa_2$ EDTA was less efficient than IV or IM therapy in correcting abnormalities in prophyrin metabolism during acute lead intoxication. Oral $CaNa_2$ EDTA given when lead is present in the gastrointestinal tract was considered by that investigator to be a dangerous drug due to the increased gastrointestinal absorption of the lead chelate. A case was described of a child who was mistakenly given oral $CaNa_2$ EDTA when his gastrointestinal tract contained lead: shortly thereafter he became comatose and developed convulsions followed by permanent and severe neurologic damage.

Current knowledge and opinion concerning the problem of occupational lead exposure including the use of chelating agents in the therapy of lead intoxication was reviewed once more in 1961.[22] $CaNa_2$ EDTA was considered particularly useful in the treatment of acute phases of lead intoxication. The reviewer considered that the routine use of this drug as a prophylactic measure to prevent lead absorption could not be condoned. He also concluded that medical measures could not be recommended as a substitute for adequate engineering measures to control lead exposure. Other authors of the period also warn against the unknown hazards of prolonged chelation therapy.

The toxic effects of EDTA were reviewed again in 1963.[23] Concern was expressed as to the possible effects of prolonged administration of EDTA upon trace metal depletion in the body. The most frequent and important side effect associated with EDTA was considered to be renal damage. Vacuolization of renal tubular

cells resembling those seen in sucrose nephrosis had been observed at autopsy in two patients given disodium EDTA in the treatment of hypercalcemia. Both patients died in renal failure following a 4-day course of treatment with EDTA. A number of autopsy studies had also demonstrated acute tubular necrosis in patients given EDTA for treatment of lead poisoning. Clinical signs of kidney damage associated with EDTA included hematuria, proteinuria, polyuria and elevated BUN levels. Subsequent to these clinical reports, studies in rats confirmed that nephrosis could be produced by administration of the drug; the lesions appeared to be reversible upon cessation of the drug administration. The reviewer expressed the need for caution in the use of this drug, and for patients receiving this medication to be under continued medical evaluation.

The treatment of heavy metal poisoning and the use of chelating agents, including penicillamine, was reviewed once more in 1970.[24]. In this assessment oral administration of $CaNa_2$ EDTA was not considered warranted in the treatment of heavy metal poisonings. The principal adverse side effect of $CaNa_2$ EDTA therapy was believed to be damage to the kidneys, particularly massive tubular necrosis. Abnormalities in cardiac electrical conductivity had also been observed during administration of this drug. Also, it was noted that monitoring of kidney function before and during administration of the drug was necessary. With the use of penicillamine, the side effects observed were nephrotic syndrome, leukopenia, neutropenia, coagulation deficits, erythematous rashes, altered collagen metabolism and fever. Penicillamine therapy in persons with chronic renal insufficiency was considered to be contraindicated.

In 1975 the subject of chelation therapy among occupationally lead-exposed workers was reviewed again.[25] The conclusion was that chelation therapy was useful for the treatment of lead poisoning but that prophylactic use of chelation therapy was contraindicated for several reasons. These included the concern about the potential for increased lead absorption from the gastrointestinal tract when oral EDTA was used; an unsatisfactory response in reducing body load of metabolically active lead; the development of symptomatic lead poisoning among some workers receiving prophylactic chelation therapy; and adverse effects of chelation therapy upon the metabolism of trace metals other than lead and upon metal-dependent enzyme activity. In addition there was concern that the two most commonly used chelating agents, EDTA and penicillamine, had the potential to cause kidney damage and/or blood abnormalities.

recent studies and related actions

Recent data from a study in the United States of workers employed at two secondary smelters in the Indianapolis area support these concerns about chelation therapy.[26] Approximately 150 workers exposed to lead were examined. Based upon results from blood lead analyses, about 30 percent were found to have blood lead levels in the range of 80 to 100 $\mu g/109$ and most workers had blood lead values of 60 $\mu g/100$ g or greater. Blood lead levels in controls exposed to moderate levels of lead in a well controlled can factory were all under 60 $\mu g/100$ g.

Approximately half of the workers studied had received at least one course of chelation therapy. Evidence of neurologic damage based either upon weakness of extensor muscles in the hands or a history of neurologic damage was found in approximately one-quarter of workers studied. Neurologic damage became evident as early as 2-3 years following onset of lead exposure. About one-quarter of the workers studied had a history of lead colic; many had more than one episode. Elevated BUN's were also observed in some of these workers. Eight workers had been hospitalized for lead poisoning. ZPP (zinc protoporphyrin) levels among these workers were extraordinarily elevated with values well in excess of 500 $\mu g/100$ ml reported. While blood lead levels generally remained under 100 $\mu g/100$ g as a result of chelation, ZPPs appeared to remain elevated despite chelation. Evidence of anemia was also observed in some workers. Motor nerve conduction velocities indicated prolonged condition times which could not be explained by age, and which suggested that lead may accelerate aging of the nervous system. These data indicated that chelation therapy may not protect against the progression of neurologic

TABLE I
Summary of the Beneficial and Adverse Effects Associated with Chelation Therapy in Man

Category	Observed Effect	References
Beneficial	Increased excretion of lead from the body and/or reduction in blood lead levels	3-8, 20
	Decrease in symptoms following treatment	4,5, 7-10, 22,25
	Generally tolerated therapy well	7,9,19
	Advocate of prophylactic chelation	18, 19
Adverse	Symptoms observed during therapy in at least some workers	3, 7, 19, 25
	Increased absorption of lead from the gastrointestinal tract	3, 7, 21, 25
	Imbalance in metabolism of metals other than lead	17, 25
	Electrocardiograph changes	4, 24
	Return of symptoms following chelation	9
	Elevated blood lead level following treatment	5, 7, 8, 20
	Therapy associated with kidney damage	11, 13-16, 19-21, 23-26
	Neurologic, hematologic or other damage associated with long term therapy particularly under conditions of continued lead exposure	18, 26
	Therapy associated with severe neurologic damage	21
	Death associated with therapy	7, 23
	Warning against prophylactic use	8,9,17,20,22,23,25

damage or against metabolic and other effects caused by lead.

Recent government actions also reflect concern about prophylactic chelation therapy. Both the National Institute for Occupational Safety and Health and the Food and Drug Administration oppose prophylactic chelation therapy, including such use of EDTA and penicillamine.[27-29]

summary and conclusions

Table I presents a summary of the beneficial as well as the adverse effects associated with chelation therapy. Chelating agents are generally effective in lowering blood lead levels and are indicated in the therapy of acute lead intoxication. However, the data presented above raise serious questions as to the safety of prophylactic chelation therapy particularly under conditions of continued lead exposure. Prophylactic chelation is defined both a) as the routine use of chelating or similarly acting drugs to prevent elevated blood lead levels in workers who are occupationally exposed to lead; or b) as the use of these drugs to routinely lower blood lead levels to predesignated concentrations believed to be "safe". Although the use of chelating agents is justified in acute lead intoxication, particularly in children, evidence does not exist to justify their use on a prophylactic basis.

The potential for chronic administration of chelating agents to cause kidney damage is a special concern. Adverse effects from chelating agents have been observed following both oral and intravenous administration. Both $CaNa_2$ EDTA and penicillamine have the potential to cause harm. The prevailing medical opinion is strongly opposed to the use of chelating agents on a prophylactic basis. Whenever chelating agents are used, there is a need for close medical supervision including careful evaluation of renal function. Death and severe injury during and following use of chelating agents have been reported in the medical literature.

Prophylactic administration of $CaNa_2$ EDTA by whatever route under conditions of continued lead exposure constitutes a particularly hazardous practice. Use of chelating agents is not an adequate substitute for engineering controls and proper industrial hygiene and work practices. Both lead and $CaNa_2$ EDTA in sufficient doses are toxic to the kidneys. Prophylactic chelation may decrease the ability of the kidneys to protect themselves against the toxic effects of lead. A recent mortality study of workers exposed to lead, for example, demonstrated an increase in deaths from end stage renal disease.[30]

In conclusion, prophylactic use of chelation to control lead absorption represents an unacceptable medical practice that cannot be condoned.

references

1. **Carnow, Bertram A., M.D.:** *Sources of Lead in Industry Monitoring of Workplace and Problems Involved, Health Effects of Occupational Lead and Arsenic Exposure* — A Symposium, U.S. Department of Health, Education and Welfare, PHS, CDC, NIOSH, pp. 24-25, February, 1975.
2. **Glasser, Melvin A.:** Director, Social Security Department, United Auto Workers, Letter to Dr. John Finklea, Director, National Institute for Occupational Safety and Health, January 6, 1976.
3. **Sidbury, J.B., Jr., J.C. Bynum and L.L. Fetz:** Effect of Chelating Agent on Urinary Lead Excretion. Comparison of Oral and Intravenous Administration. *Proc. Soc. Exper. Biol. Med., 82:*226 (1953).
4. **Bradley, J.E. and A.M. Powell, Jr.:** Oral Calcium EDTA in Lead Intoxication of Children. *Pediatr. 45:*297 (1954).
5. **Manville, I.A. and R. Moser:** Recent Developments in the Care of Workers Exposed to Lead. *A.M.A. Arch. Ind. Health 12:*528 (1955).
6. **Bell, R.F., J.C. Gilliland, J.R. Boland and B.R. Sullivan:** Effect of Oral Edathamil Calcium-Disodium on Urinary and Fecal Lead Excretion, *A.M.A. Arch. Ind. Health 13:*366 (1956).
7. **Shiels, D.O., D.L.G. Thomas and E. Kearley:** Treatment of Lead Poisoning by Edathamil Calcium-Disodium. *A.M.A. Arch Ind. Health 13:*489 (1956).
8. **Williams, J.D., G.A. Matthews and A.W. Judd:** Oral Calcium Disodium Versenate in Treatment of Lead Poisoning. *Brit. J. Ind. Med. 19:*211 (1962).
9. **Sidbury, J.B., Jr.:** Lead Poisoning - Treatment with Disodium Calcium Ethylenediamine-tetra-acetate. *Am. J. Med. 18:*932 (1955).
10. **Cotter, L.H.:** Treatment of Lead Poisoning by Chelation. *J.A.M.A.* pp. 906-908, July 3, 1954.
11. **Selender, S., K. Cramer and L. Hallberg:** Studies in Lead Poisoning-Oral Therapy with Penicillamine: Relationships between Lead in Blood and other Laboratory Tests. *Brit. J. Ind. Med. 23:*282 (1966).
12. **Doolan, P.D. et al:** An Evaluation of the Nephrotoxicity of Ethylenediaminetetraacetate and Diethylenetriamine-pentaacetate in the Rat. *Toxicol. Appl. Pharmacol. 10:*481 (1967).
13. **George, I.M.:** Two Men with Lead Poisoning, *N.Z. Med. J. 71:*294 (1970).
14. **Goyer, R.A. and M.H. Wilson:** Lead-Induces Inclusion Bodies — Results of Ethylenediaminetetraacetic Acid Treatment. *Lab. Invest. 32:*149 (1975).
15. **Cramer, K. et al:** Renal Ultrastructure, Renal Function and Parameters of Lead Toxicity in Workers with Different Periods of Lead Exposure. *Brit. J. Ind. Med. 31:*113 (1974).
16. **Chisolm, J. J.:** The use of Chelating Agents in the Treatment of Acute and Chronic Lead Intoxication in Childhood. *J. Pediatr. 73:*1 (1968).
17. **Kehoe, R.A.:** Misuse of Edathamil Calcium - Disodium for Prophylaxis of Lead Poisoning. *J.A.M.A. 157:*341 (1955).
18. **Burnett, J.M.:** The Prevention of Lead Poisoning with Oral Calcium Disodium Versenate. *Ala. Gen. Pract. 9:*6 (1959).
19. **Holt, R.:** Diagnosis and Treatment of Lead Absorption in Industry, *Southwest. Med.* pp. 328-332, June 1958.
20. **Miller, L.H.:** EDTA Therapy in Persons with Excessive Lead Absorption from Industrial Exposure. *Ind. Med. Surg. 28:*144 (1959).
21. **Byers, R.K.:** Lead Poisoning - Review of the Literature and Report on 45 Cases. *Pediat. 23:*585 (1959).
22. **Skinner, J.I.:** The Lead Problem - An Outline of Current Knowledge and Opinion. *J. Occup. Med. 9:*429 (1961).
23. **Foreman, H.:** Toxic Side Effects of Ethylenediaminetetraacetic Acid. *J. Chron. Dis. 16:*319 (1963).
24. **Chisolm, J.J.:** Poisoning Due to Heavy Metals. *Ped. Clin. N.A. 17:*591 (1970).
25. **Lilis, R. and A. Fischbein:** Chelation Therapy in Lead-Exposed workers - A Critical Review, Presented at the International Conference on Heavy Metals in the Environment, Toronto, Canada, Oct. 27-31, 1975.
26. *Lead Disease Among Workers in Secondary Lead Smelters: Results of a Clinical Field Survey February 2-4, 1976,* Report to the National Institute of Environmental Health Sciences, Environmental Sciences Laboratory, Mount Sinai School of Medicine, New York, New York.
27. **Foley, Patricia:** NIOSH/HEW Press Release on Lead and Chelating Agents, March, 1976.
28. FDA Memorandum on penicillamine, Department of Health, Education, and Welfare, May 28, 1976.
29. *Lead Poisoning and Misuse of Chelating Agents,* FDA Drug Bulletin, Vol. 6, No. 3, June-July, pp. 26-28.
30. **Cooper, W.C. and W.R. Gaffey:** Mortality in Lead Workers. *J. Occup. Med. 17:*100 (1975).

Accepted May 2, 1977