TETRACHLORETHYLENE AS AN ANESTHETIC AGENT *

ELLEN B. FOOT, M.D.; KINGSLEY BISHOP, M.D.,† AND VIRGINIA APGAR, M.D.

New York City

THE need for a potent, portable, non-toxic, non-inflammable and non-explosive anesthetic agent for use in the armed forces has added impetus to the continuous search for such a drug. It is not possible in any brief statement to evaluate the intrinsic merit of the commonly used general anesthetic agents, nor to mention more than the outstanding disadvantages of each, regardless of their relative importance. Although nitrous oxide satisfies the criteria of non-explosibility and non-toxicity, its lack of potency and portability limits its usefulness. The other gaseous agents, ethylene and cyclopropane, though more potent than nitrous oxide, are no more portable, and their explosibility makes them decidedly less suitable for war conditions. Ether, vinethene and ethyl chloride require no more apparatus than an open drop mask, and so are portable as well as potent, but may be an ever present fire hazard. The latter two agents fail to be sufficiently non-toxic for use in prolonged or deep anesthesias. There remains one volatile agent, chloroform, which is not only potent and portable, but also non-inflammable. The toxicity to heart and liver, however, is of such severity and frequency that its advantages are outweighed. The rectal agents can be used with safety when the dosage is estimated to produce a basal narcosis and a supplement is planned. When doses calculated for surgical anesthesia are given, unpredictable variations in absorption may result in fatal overdoses in some instances, and in others anesthetic failure. Avertin, the agent most commonly used by this route, also has the disadvantages of vasomotor depression and hepatic and renal toxicity. The intravenous administration of short-acting barbiturates for general anesthesia is considered by many to be the nearest approach to the ideal as we have defined it. The shallow respirations, mediocre relaxation, narrow margin of safety between surgical anesthesia and overdose, and prolonged depression after large doses do not permit the use of this agent for all varieties of cases, ideal as it may be for peripheral and superficial procedures of relatively short duration. For many types of surgery local or regional anesthesia has proved entirely satisfactory. Situations may arise, however, where none of these technics is applicable because of the presence of infection, the site, extent, and duration of the procedure necessary, or the patient's

* From the Division of Anesthesia, Department of Surgery, Presbyterian Hospital, New York City.

† Now located at Philadelphia General Hospital, Philadelphia, Pa.

general status. The relief of pain and relaxation may be achieved by the block, yet, since many war casualties are psychically unfit for local or regional anesthesia, one of the general anesthetics may be needed to abolish consciousness.

This preliminary study was undertaken to reëvaluate the anesthetic possibilities of tetrachlorethylene, a non-explosive agent known to have narcotic properties, and known to be one of the least toxic of the halogenated hydrocarbons. When halogen groups are substituted in members of the aliphatic series, distinct changes in both physical and pharmacological properties (1, 2, 3, 4) occur. The saturated and unsaturated series are not strictly comparable. There is evidence that the unsaturated hydrocarbons are less toxic than the saturated when halogenated; and that whereas toxicity has a direct qualitative relation to the number of halogen groups in the saturated series, this relation is inversely proportional in the unsaturated one (4). For example: it is known that carbon tetrachloride is more toxic than chloroform, while animal studies suggest that tetrachlorethylene is less toxic than trichlorethylene.

Tetrachlorethylene (5) (CCl_2: CCl_2) (synonym: perchlorethylene) is a heavy, colorless liquid (molecular weight 165.83; specific gravity 1.6; chlorine content 85.5 per cent) with a slightly sweet hydrocarbon odor. It is non-inflammable as well as non-explosive, and is stable when kept in amber bottles. After excessive exposure to ultra-violet light and heat, phosgene and hydrochloric acid may be formed in small amounts. The vapor of tetrachlorethylene is heavier than air (vapor density 5.72), and vaporization will occur at room temperature, though the volatility of the liquid is limited by its relatively high boiling point (121 C.). The ratio of the oil-water solubility for this substance is high, but cannot be expressed in a definite number as is conventionally done for other anesthetics, since it is miscible with animal, vegetable, and mineral oils in all proportions. The water solubility is extremely low (0.4 gram/liter at 30 or 1: 2,500). Its present uses are (1) as an industrial degreasing agent (6), where the above mentioned properties make it highly efficient, and (2) as an anthelmintic (7, 8), especially for Necator americanus (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19). In both uses a large number of human beings has been exposed to the chemical. In the industrial group the exposure is by inhalation to low concentrations over long periods of time. Carpenter (6) reports an average concentration of 47 parts per million (0.32 mg./liter) in two plants with modern equipment, and a maximum average concentration of 280 p.p.m. (1.9 mg./liter) in an older plant, where the same operator had been working for two years. The group treated for helminthiasis is exposed by ingestion of single doses, or of multiple doses within a few days. (Adult oral dose 2–6 cc.)

The narcotic properties of tetrachlorethylene were first investigated in 1911 and again in 1936 by Lehmann (1, 3) and his associates. Using

cats as test animals they determined the time in which varying concentrations of the drug produced light and deep narcosis. Less than 20 mg./liter (3000 p.p.m.) produced no anesthesia in four hours, and concentrations of about 100 mg./liter (14,600 p.p.m.) anesthetized the animals in one to two hours. The use of the drug as an anthelmintic was first suggested by Hall and Shillinger in 1925 (9, 10). Because of its increasing use for this purpose, in 1929 Lamson, Robbins and Ward (2) studied the pharmacology of tetrachlorethylene extensively. Using the method of thermal conductivity for analysis of gas samples they determined that in dogs a concentration in inspired air of 62 mg./liter (9000 p.p.m) was necessary to produce anesthesia. This concentration also caused the secretion of large amounts of saliva (300 cc. in five hours). The usual stages of anesthesia were reproduced, but it was almost impossible to obtain muscular relaxation with any concentrations except nearly fatal ones. These workers, and also Schlingman and Gruhzit (20), and others (21, 22), found the drug to cause few metabolic or physiological changes. All reports agreed that, unlike the saturated halogen-containing aliphatic hydrocarbons such as chloroform and carbon tetrachloride, necrosis of the liver and kidneys does not occur after exposure to tetrachlorethylene. Lamson (2) reported a series of approximately 400 animal experiments: 116 animals (puppies, cats, rabbits, and mice) were examined for pathological changes in liver and kidneys after oral doses up to 25 cc. per kg. or after five to six hours of inhalation at a depth of surgical anesthesia. In a few animals, principally puppies and kittens, there was a mild degree of fatty infiltration of the liver, but necrosis was absent in all instances, the fatty infiltration being no more than in the control animals on the same diet. In 10 dogs (5 by oral dosage, 5 by inhalation anesthesia) excretion of dye by the liver was essentially normal. In 35 dogs and 8 cats (oral and inhalation) the drug caused no change in icteric index. After oral doses in 31 dogs the blood fibrin content showed no fall, as is seen after administration of chloroform and carbon tetrachloride. There was no change in blood sugar or blood guanidine in 4 dogs and 6 cats. Specimens of the urine of 4 dogs (oral doses) were normal in amount, specific gravity and reaction, and negative for sugar, albumin, acetone, bile and cellular elements. Phenolsulfonphthalein tests in 2 dogs showed normal urinary excretion of the dye. One hundred and eighty-five animals (dogs, puppies, cats, rabbits, mice and guinea pigs) were killed by oral overdosage, and in every instance death was due to irreversible narcosis and not to any demonstrable pathological change in the vital organs.

The narcotic action in humans has been observed by several industrial workers (6, 23), while studying the toxic effects of the drugs used in cleaning industries. We have not found any reports of the clinical use of tetrachlorethylene as a narcotic or anesthetic agent. The recent report most pertinent to our study is that of Carpenter (6), in 1937.

He and three co-workers exposed themselves to four different concentrations of the vapor in a 210 cu. ft. chamber and observed their subjective responses. At all concentrations pulse rates remained normal and examinations of the urine were uniformly negative. At 50 parts per million (0.36 mg./liter) the odor of the drug was detectable. At 100 p.p.m. (0.68 mg./liter) increased salivation, lacrimation, and increased perspiration were noted, appetite usually seemed to be increased but occasional nausea occurred, and in one subject a feeling of inebriation was present. At 1000 p.p.m. (6.8 mg./liter) mental fogginess and lassitude were added to the above symptoms. At this concentration the only circulatory change found in this study occurred: one subject showed a moderate but definite drop in blood pressure without any rise in pulse rate. At 2000 p.p.m. (13.4 mg./liter) faintness was present within five to seven minutes, after which time the subjects left the chamber lest they lose consciousness. These responses coincide with the subjective sensations of any first stage anesthesia. The concentration for beginning loss of consciousness here is slightly lower than that producing prompt light anesthesia in the cats of Lehmann's series (1, 3) (3000 p.p.m.), and much less than the concentration Lamson reports for dogs (9000 p.p.m.). For several hours after Carpenter's experiment dyspnea was present on exertion in all subjects. In one case, the odor persisted on the breath for twenty-four hours.

During the use of tetrachlorethylene in over 50,000 human beings as an anthelmintic (7, 8, 11, 12, 13, 15, 16, 18, 24), most of the "toxic reactions" reported are manifestations of its narcotic properties. Many clinical investigators mention giddiness and drowsiness as the characteristic minor toxic symptoms (7, 12, 13, 14, 18, 19, 23, 24, 25, 26, 27). These symptoms are more likely to be accentuated in children because the intestinal absorption of the drug is apparently greater in them than in adults. The only reactions reported besides this narcotic effect were nausea and occasional vomiting, which may have resulted from the irritating action of the drug on the gastric mucous membrane. A group of patients reported by Gunewardne (28) showed a generalized reaction to the oral use of the drug from a single bottle, which was characterized by a rapid pulse, fast shallow respirations, and pale cold skin. Two children required supportive treatment with caffeine, camphor and pituitrin, but no fatalities occurred. The author attributed this reaction to an impurity in the drug rather than to the drug itself, because when a sample from the bottle used was submitted to the Indian Government Laboratory for analysis, the presence of phosgene was reported.

PRESENT STUDY

Animals.—Since the toxicology of tetrachlorethylene in animals has been so thoroughly investigated by Lamson, Robbins, and Ward, no attempt was made here to duplicate their excellent series. All reports

available in the literature indicate that this drug in its pure state does not exert the same toxic effects on parenchymatous organs that are seen with the chlorinated members of the saturated hydrocarbon series. The tetrachlorethylene ("perchlorethylene") used in this study was generously supplied by the DuPont Chemical Company in a highly purified form, and was stored in 250 cc. brown glass bottles with screw caps of plastic material. The product had already been investigated in the Haskell Laboratories of this company in a series of experiments for chronic toxicity on dogs, with results agreeing with those reported by others. We re-checked the drug for anesthetic potency and toxicity in a small series of 18 acute experiments with guinea pigs. This species is reported by Smyth, Smyth and Carpenter (29) to be peculiarly susceptible to hepatic and renal damage from chlorinated hydrocarbons, and to be prone to a high incidence of pulmonary disease when used in the study of such drugs. Despite these tendencies our animal group survived the anesthesias without impairment of appetite or activity, and those given daily exposures remained lively throughout the test period. During none of the inductions was there evidence of generalized collapse such as was seen in Gunewardne's patients when partially decomposed tetrachlorethylene was administered. The animals struggled briskly at first, then gradually progressed to surgical anesthesia with abolition of reflexes and response to pain stimulation, and depression of muscle tone. Recovery was in the reverse order with transient ataxia as the final symptom. The sequence of signs of anesthesia differed in no way from that seen when ether is given to the same species. In all the anesthetized animals, because of the accumulation of mucus, anoxia was a possible toxic factor. This would be expected to exaggerate any tendency toward liver damage if the situation is comparable to the production of liver necrosis by anoxia during nitrous oxide (30) or vinethene anesthesia (31).

Two guinea pigs were anesthetized by the open drop method to a deep plane of anesthesia for twenty minutes, daily, for seven days. They were given no premedication, and were allowed their usual diet when returned to their cages on recovery. After a seven day interval they were killed by bleeding. Another group of unpremedicated guinea pigs was anesthetized deeply by the same method, and kept in deep surgical anesthesia for one hour. They were returned to their cages on recovery, and 1 was killed by bleeding after each of the following survival periods: twenty-four, forty-eight, seventy-two and ninety-six hours. Postmortem examinations were done on all of the animals, and no gross pathological changes were present. Sections of myocardium, lung, spleen, kidney, and liver were submitted to Dr. James W. Jobling, who found the specimens of myocardium, lung, spleen, and kidney entirely normal. There was slight fatty infiltration of the liver, though this was present to the same degree in 4 unanesthetized control animals on the same diet.

Humans.—Four healthy adult volunteers were lightly anesthetized (II stage, or 1st plane III stage) with tetrachlorethylene, 1 of these having received it three times. Recovery was prompt and uneventful in all instances, except for the burn at the canthus of the eye mentioned below. It was subsequently administered to a depth of surgical anesthesia to 14 patients (see table). Only those patients were chosen who presented an entirely healthy preoperative status and in whom the surgical procedure planned demanded no greater depth of anesthesia than loss of consciousness. None was carried deeper than second plane of the third stage of anesthesia. Infants and elderly individuals were not included in the series, the range in age being 2 to 48 years. The open drop method, oropharyngeal insufflation with oxygen, and the circle absorption technics were used. All subjects agreed that the odor was not objectionable if the concentration was not increased too rapidly. Excessive lacrimation and salivation were a constant accompaniment of anesthesia, but could be prevented by appropriate doses of atropine or scopolamine. Loss of consciousness was quick, but considerable time was needed to deepen the anesthesia. Even after forty-five minutes with a closed absorption system, a subject could not be anesthetized below the second plane, because the active cough reflex prevented the assimilation of higher concentrations. The actual concentration of tetrachlorethylene in inspired air was not determined in this preliminary series. Surgical anesthesia was induced after 5–15 cc. had been dropped slowly on an open mask, but since the liquid volatilized much less rapidly than the same amount of ether or chloroform, this quantity was far in excess of that inhaled by the patient. The absorption of the vapor by the lungs is greater than the absorption of the liquid by the gastrointestinal tract; therefore it is not surprising that, while 2–6 cc. by mouth only occasionally resulted in drowsiness, the inhalation of the vapor from approximately 5 cc. produced anesthesia. Nitrous oxide was added twice (see table) as a supplemental agent because of the time-consuming induction below the second stage. Good surgical relaxation was not obtained in the third stage. In 2 cases open drop ether (see table) was administered for a few minutes after second plane, third stage had been reached with tetrachlorethylene, and the latter drug was resumed after relaxation had been produced. This relaxation, however, was transient despite maintenance at the same depth of anesthesia. In some instances, both with human and animal subjects, the incomplete relaxation may in part have been due to hypoxia and retention of carbon dioxide resulting from the accumulation of secretions. It is possible that the same situation obtained when other workers (Lamson, et al.) (2) found relaxation inadequate in animal experiments. The drug was noted to be a definite respiratory stimulant even with a patent airway. All cases exhibited an increase in respiratory rate (see table) which became more pronounced as the anesthetic depth increased. The rapid respiratory rate was not correlated with the

TABLE OF CASES

	Sex and Age	Premedication	Technic	Added Agents	Operation	Duration of Anesthesia	Remarks
1	M—child	None	Open	None	Circumcision	Short	No anesthesia record available
2	M—child	None	Open	None	Circumcision	Short	Burn of cheek—no record of anesthesia
3	?—child	Seconal and scopolamine	Open	None	Cystoscopy	Short	No anesthesia record available
4	M—3 yrs.	Seconal and scopolamine	Open	None	Cystoscopy	20 min.	Maximum respiratory rate 60/minute
5	M—5½ yrs.	Seconal and scopolamine	Open	None	Cystoscopy	20 min.	Cyanosis during anesthesia; maximum respiratory rate 50/minute
6	F—6½ yrs.	Seconal and scopolamine	Open	None	Cystoscopy	30 min.	Maximum respiratory rate 50/minute
7	F—2 yrs.	Seconal and scopolamine	Open	Oropharyngeal-oxygen	Cystoscopy	25 min.	Pulse rise from 90 to 130/minute. Maximum respiratory rate 60/minute
8	F—6½ yrs.	Seconal and scopolamine	Open	Ether—few minutes	Cystoscopy	25 min.	No pulse rise; respirations not recorded
9	M—12½ yrs.	Seconal and scopolamine	Open	Ether—few minutes	Cystoscopy	45 min.	Burn on cheek; maximum respiratory rate 50/minute
10	F—27 yrs.	Seconal and scopolamine	Open	None	Breech delivery, episiotomy	30 min.	Conjunctivitis post-anesthesia. Baby cried promptly; fundus firm post-delivery. Maximum respiratory rate 54/minute
11	M—11 yrs.	Seconal and scopolamine	Oropharyngeal insufflation	Oxygen	Orchidopexy	1'10"	Maximum respiratory rate 90/minute
12	F—32 yrs.	Morphine and scopolamine	Semi-closed	Nitrous oxide induction; oxygen	Excision lipoma of arm	1'30"	Laryngospasm during anesthesia. Respiratory rate increased from 18 to 28/minute
13	M—47 yrs.	Morphine and atropine	Closed—circle-absorption	Nitrous oxide induction; oxygen	Exploration of tendon sheath of hand	1'15"	B.P. rise from 110/80 to 140/90. Maximum respiratory rate 50/minute
14	M—18 yrs.	Morphine and scopolamine	Closed—circle-absorption	Oxygen	Removal of fixation bolt from ankle	55 min.	Respiratory rate increased from 18 to 36/minute

Case No. 7: only pulse rise of 11 cases who had pulses recorded on chart.
Case No. 13: only B.P. change (rise) of 5 cases who had B.P. recorded.
Cases No. 4, 5, 6, 7, 9, 10, 11 and 13: respiratory rate of 50/minute or more during second plane.
Cases No. 12 and 14: increase in respiratory rate not exceeding 40/minute.
Cases No. 12, 13 and 14: Morphine premedication failing to prevent increase of respiratory rate.

presence or absence of mucus in the respiratory passages, nor with low or high concentrations of oxygen in the inspired mixture. The fastest respirations recorded occurred in patient No. 11 (see table) who was anesthetized by oropharyngeal insufflation of the vapor with oxygen throughout. Recovery from the anesthesia in each instance was as prompt as would be expected after an ether anesthesia of comparable depth and duration. There were no postanesthetic complications in this small group referable to the gastrointestinal or circulatory systems, nor to the respiratory tract, despite the excessive secretions caused by the drug.

The chief difficulties encountered were those of a technical nature. It was impossible to secure rapid, efficient vaporization of the drug, as might be suspected from its boiling point. (Lamson also states this difficulty in his report of animal anesthesias.) In using the open drop technic it was noted that: a mask saturated with the liquid drug remained wet for four to five hours; the tidal volume of a normal adult was not great enough to vaporize the drug on the gauze mask; and additional heat, in the form of hot towels around the mask, was ineffectual in increasing vaporization. Considerable practice was found necessary to perfect a satisfactorily smooth insufflation technic where large volumes of air or oxygen are passed through the drug to vaporize it. In a circle absorption system in which the drug is added from a drop-cup, a truly closed system could not be achieved since such a rapid flow of oxygen was needed for vaporization of the drug that the exhalation valve had to remain open throughout. The vapor was potent enough, however, to maintain second plane anesthesia despite the high dilution with oxygen. The canister, bag, tubing and mask of the machine thus used retained a distinct odor of tetrachlorethylene for long periods after the drop-cup was emptied, indicating that lightening of the anesthesia might be considerably impeded if a closed system were maintained. The slow vaporization, therefore, deprives the drug of the outstanding advantage of most inhalation agents, namely "moment to moment" control of the depth of anesthesia.

This slow vaporization was also the cause of a distressing complication in 4 of the 20 administrations: various types of face burns resulted from contact with the vapor. It is certain that no liquid drug caused the burn in any case, but all instances occurred when prompt dissipation of the vapor was prevented by the covering of an area after exposing it to the vapor. In one volunteer, a second-degree burn occurred at the outer canthus of the eye which had shown excessive lacrimation during induction, the area burned having been covered by a film of moisture. One patient (case No. 2) was burned under an area of saliva which had not been removed quickly enough. In another patient (case No. 9), a first-degree burn which persisted for two days after anesthesia developed in the area which had been covered by the anesthetist's left hand in holding the mask on the face. In the fourth in-

stance (case No. 10), the subject suffered a conjunctivitis in the eye which had been inspected most frequently during anesthesia, the lid having been closed between observations. The face of this patient was washed with soap and water at the termination of anesthesia, which may have prevented the development of a skin burn around the eye involved. The high incidence of this complication alone is a strong contraindication to the administration of tetrachlorethylene by the open drop, and possibly also by the closed technic.

SUMMARY AND CONCLUSIONS

Tetrachlorethylene is a non-inflammable, non-explosive anesthetic agent, capable of producing in human beings a moderate depth of surgical anesthesia, though not marked surgical relaxation. It is probable that it has considerable potency since ample oxygenation of the subject does not lighten the plane of anesthesia. Available data on studies on animals and human beings indicate that it is non-toxic. After use of the drug as an anesthetic agent no systemic reactions were evident clinically in a small series of human subjects, but several superficial burns of the face occurred. Because of its irritant effect on mucous membranes, it is not likely that postanesthetic pulmonary complications would be reduced by the use of this drug. The difficulties of vaporization present an almost insurmountable problem. It seems unjustifiable to continue the use of tetrachlorethylene for anesthesia in human subjects, since the chief advantages of portability, non-inflammability and non-explosibility do not outweigh the disadvantages of the drug.

REFERENCES

1. Lehmann, K. B.: Experimental Studies of Inhalation of Technically and Hygienically Important Gases and Vapors on the Organism, Arch. f. Hyg. 74: 1–60 (April) 1911.
2. Lamson, P. D.; Robbins, B. H., and Ward, C. B.: Pharmacology and Toxicology of Tetrachlorethylene, Am. J. Hyg. 9: 430–444 (March) 1929.
3. Lehmann, K. B., and Schmidt-Kehl, L.: The Thirteen Most Important Chlorinated Aliphatic Hydrocarbons from the Standpoint of Industrial Hygiene, Arch. f. Hyg. 116: 131–268 (June–July) 1936.
4. Haskell Laboratories: Personal communication.
5. Council Report: Tetrachlorethylene, J. A. M. A. 107: 1132–1133 (Oct. 3) 1936.
6. Carpenter, C. P.: The Chronic Toxicity of Tetrachlorethylene, J. Indust. Hyg. & Toxicol. 19: 323–336 (Sept.) 1937.
7. Wright, W. H.; Bozicevich, J., and Gordon, L. S.: Studies on Oxyuris: V. Therapy with Single Dose of Tetrachlorethylene, J. A. M. A. 109: 570–573 (Aug. 21) 1937.
8. Wright, W. H.; Bozicevich, J., and Gordon, L. S.: Clinical Improvement after Treatment with Single Dose of Tetrachlorethylene in Oxyuriasis, Am. J. Trop. Med. 18: 609–617 (Sept.) 1938.
9. Hall, M. C., and Shillinger, J. E.: Tetrachlorethylene, A New Anthelmintic for Worms in Dogs, North Am. Vet. 6: 41–52 (Jan.) 1925.
10. Hall, M. C., and Shillinger, J. E.: Tetrachlorethylene, A New Anthelmintic, Am. J. Trop. Med. 5: 229–237 (May) 1925.
11. Fernando, P. B.; D'Silva, M.; Stork, G. E. B., and Sinnatamby, S. R.: Toxicity of Tetrachlorethylene in Treatment of Hookworm Disease, Indian J. M. Research 26: 759–783 (Jan.) 1939.
12. Kendrick, J. F.: Treatment of Hookworm Disease with Tetrachlorethylene, Am. J. Trop. Med. 9: 483–488 (Nov.) 1929.

13. Lambert, S. M.: Hookworm Disease in the South Pacific, J. A. M. A. 100: 247–248 (Jan. 28) 1933.
14. Maplestone, P. A., and Mukerji, A. K.: Tetrachlorethylene in Treatment of Hookworm Disease, Indian M. Gaz. 68: 617–620 (Nov.) 1933.
15. Garrison, H. F.: A Comparative Study of the Value of Tetrachlorethylene as a Means of Ultimate Control and Eradication of Hookworm Disease in Children, South. M. J. 27: 24–27 (Jan.) 1934.
16. Smith, W. H. Y.; McAlpine, J. G., and Gill, D. G.: Intestinal Parasite Survey in Alabama, A Comparative Study of Two Anthelmintics, Am. J. Pub. Health 27: 471–475 (May) 1937.
17. Schapiro, L., and Stoll, N. R.: Preliminary Note on Anthelmintic Value of Tetrachlorethylene—Egg Counts, Am. J. Trop. Med. 7: 193–198 (May) 1927.
18. Soper, F. L.: Tetrachlorethylene in the Treatment of Hookworm Disease, Am. J. Trop. Med. 6: 451–454 (Nov.) 1926.
19. Manson, D.: Comparative Record of Anthelmintic Treatment with Tetrachlorethylene and Oil of Chenopodium, Indian M. Gaz. 69: 500–507, 1934.
20. Schlingman, A. S., and Gruhzit, O. M.: Studies on the Toxicity of Tetrachlorethylene, A New Anthelmintic, J. Am. Vet. M. A. 71: 189–209 (May) 1927.
21. Maplestone, P. A., and Chopra, R. N.: Toxicity of Tetrachlorethylene to Cats, Indian M. Gaz. 68: 554–555 (Oct.) 1933.
22. Christiansen, B. V., and Lynch, H. J.: Effect of Anthelmintic on Host, J. Pharmacol. & Exper. Therap. 48: 311–316 (July) 1933.
23. Oettingen, W. F. von.: The Halogenated Hydrocarbons: Their Toxicity and Potential Dangers, J. Indust. Hyg. & Toxicol. 19: 349–448 (Oct.) 1937.
24. Sharp, E. A.: Relation of Toxicity to Dosage of Tetrachlorethylene, J. Trop. Med. 33: 336–339 (Nov. 15) 1930.
25. Lamson, P. D.; Brown, H. W., and Ward, C. B.: Anthelmintics: Some Therapeutic and Practical Considerations of Their Use, J. A. M. A. 99: 292–295 (July 23) 1932.
26. Hare, K. P., and Dutta, S. C.: Comparative Value of Oil of Chenopodium and Tetrachlorethylene as Anthelmintics for Use in Mass Treatment, Indian M. Gaz. 74: 198–201 (April) 1939.
27. Sandground, J. H.: Toxicity Resulting from Medication with Tetrachlorethylene, J. A. M. A. 117: 440–441 (Aug. 9) 1941.
28. Gunewardne, S. R.: Decomposition of Tetrachlorethylene, J. Ceylon Br. Brit. M, A. 36: 22–24 (Jan.) 1939.
29. Smyth, H. F.; Smyth, H. F., Jr., and Carpenter, C. P.: The Chronic Toxicity of Carbon Tetrachloride: Animal Exposures and Field Studies, J. Indust. Hyg. & Toxicol. 18: 277–298 (May) 1936.
30. Courville, C. B.: Untoward Effects of Nitrous Oxide Anesthesia, Mt. View, Cal., Pacific Press, 1939.
31. Adriani, J.: The Pharmacology of Anesthetic Drugs, Springfield, Ill., C. C. Thomas, 1941.