THE SMALLER HALOGENATED ALIPHATIC HYDROCARBONS

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The chemical substances to be considered in this review are those compounds containing from 1 to 4 carbon atoms and 1 or more halogen atoms. Because of current interest, halogenated ethers are included, although they are not, strictly speaking, hydrocarbons. Compounds containing other functional groupings obviously excluded themselves.

The period, 1955 to June, 1961, is covered as accurately as space and frailty permit. The reader would be well-advised to study both sections, for some widely different view points are held by anesthesiologists and toxicologists.

Anesthetic Aspects

The production of general anesthesia is at least as much an art as it is pharmacological engineering. The primary criteria; that the patient should feel no pain and recover undamaged from the anesthetic and that the surgeon should be able to perform the necessary procedures, can be met by the skilled practitioner with any one of a wide variety of agents, whereas the neophyte can expect trouble with them all.

Local conditions and the skills and prejudices of the anesthetist and surgeon have as much to do with the outcome and evaluation of the anesthesia as does the special pharmacology of the anesthetic vapor employed. In truth, "What is one man's poison is another's meat."

Chloroform.—Despite its classic reputation for evil-doing, chloroform has reacquired supporters, particularly as more reliable methods of administering powerful anesthetics have been recently developed. Although earlier than our general coverage, one should still begin with the detailed Wisconsin study (1). More recently, Duncan *et al.* (2) reported some 17,000 obstetrical patients receiving chloroform alone as their obstetrical anesthetic. These investigators were well pleased with the results and reported no deaths or late toxic manifestations of hepatic and renal damage in this series. The well-known tendency of chloroform to decrease the strength of uterine contraction can indeed at times be an advantage. That the agent has intrinsic hazard even in the best hands today is indicated by the report of Siebecker & Orth (3) who attempted seven administrations in open thoracic operations. Two of the seven patients died due to acute centrilobar necrosis of the liver, and two more presented clinical and laboratory evidence of toxic hepatitis. It is probable that the poor ventilation consequent upon intrathoracic exploration was a considerable factor and they caution against the use of chloroform under such conditions. The light touch with chloroform is again emphasized by Davison (4). Lately, Dobkin, Johnston & Skinner (5) have examined chloroform using a modern temperature-compensated vaporizer. With this

equipment they found that surgical anesthesia was comfortably accomplished with less than 1 per cent chloroform in the inhaled gas stream. In a second study, Dobkin *et al.* (6) conclude that "chloroform has been inordinately maligned as an anesthetic." All authors stress the meticulous care which must be used to maintain oxygenation and prevent retention of carbon dioxide. Poe & Mayfield (7) used chloroform in 70 patients needing a nonflammable anesthetic with considerable success when attention was paid to these points and care was taken to avoid the use of chloroform in patients with liver disease. Other reports on chloroform in obstetrics were found (8, 9, 10). EEG and blood pressure correlated well with blood chloroform concentrations in any particular dog (Pearcy *et al.* 11).

Trichloroethylene.—Trichloroethylene differs from the other volatile anesthetics in that it is well-known to undergo extensive metabolism (see II and 12, 13); and in addition, is incompatible with soda lime. While the former is no fundamental drawback, the latter most emphatically is. As patients exhale trichloroethylene for some time after an anesthesia, it negates any possibility of using soda lime or similar materials for CO_2 reabsorption during an uncertain time after trichloroethylene. An open system without CO_2 reabsorption is therefore essential (14, 15). The lack of stability of the compound also suggests that possible decomposition will occur in the machine itself (16). The concentration of trichloroethylene may vary as a result of a variety of factors connected with the particular apparatus employed (17, 18).

It is often recommended for dental procedures, particularly to produce analgesia. Bergner *et al.* (19) reported several thousand successful dental procedures under quite light trichloroethylene added to nitrous oxide. A similar experience was reported by Atterbury & Borkenhagen (20) and by Boston (21). Spiro (22) reports that the patients will tolerate an endotracheal tube quite nicely under very light trichloroethylene-nitrous oxide. In all these reports, it is evident that the authors have been impressed with the necessity for light anesthesia and a delicate touch. For the "occasional" dental anesthetist, trichloroethylene certainly seems to leave something to be desired in the way of safety—though perhaps there should be no "occasional anesthetists."

There have been many reports of the effectiveness of trichloroethylene as an analgesic or anesthetic in gynecology [Siegler, (23)] and in obstetrics (24, 25, 26, 27). These latter studies vary considerably in character, ranging from trichloroethylene anesthesia to trichloroethylene analgesia supplementing nitrous oxide-oxygen. It is almost impossible to compare these studies or to draw any conclusion except that a very skilled anesthetist with competent obstetricians can use trichloroethylene with success.

In general surgery, Crankshaw (28) feels it has but one contribution to make and that is to provide a high degree of analgesia at a minimum vapor concentration. Stephen (29) remarks that in 1958, 35,000 liters of trichloroethylene were utilized in the United States for analgesic and anesthetic purposes, but that "the learning process regarding the value of trichloro-

ethylene has been painful." Norris & Stuart (30) feel that the place of trichloroethylene in modern anesthesia is very limited and report seven previously unpublished cases of cardiac arrest during such anesthesia. Cardiac damage leading to arrhythmias following non-anesthetic exposures was studied by Dhuner *et al.* (31). Light anesthesia for major surgery utilizing trichloroethylene is described by Rahter (32) but so many premedications and adjuncts are employed that it almost seems not to require the trichloroethylene. The lack of explosiveness of trichloroethylene has recommended its use in neurosurgery [*v.* König (33)] and the related area of opthalmic surgery where Tennent of New Zealand (34) finds it efficacious.

An extensive review on trichloroethylene anesthesia by Atkinson (35) which appeared in 1960 contains many other references and his own experience with trichloroethylene. He concludes that it has a significant place in anesthesia and that the disadvantages have been overcome with increasing experience.

Methylchloroform.—The very low toxicity of this compound, 1,1,1-trichloroethane is discussed in II. The anesthetic properties have been described by Krantz, Park & Ling (36) in the dog and monkey. Although anesthesia was satisfactory in many respects, they suggested cautious approach to its trial in man. According to Siebecker *et al.* (37), it is distinctly less potent clinically than chloroform and, in supplementing nitrous oxide-oxygen, less potent than trichloroethylene, but the depression of the circulation was much greater than the depression of the central nervous system. Dornette & Jones (38) examined this material as an anesthetic in fifty patients. After noting some of its advantages, they point out the disadvantage of marked depression of circulation and the tendency to develop ventricular rhythms at low concentrations which barely produce adequate anesthesia. It is their impression "that the disadvantages of this compound outweigh its advantages."

Methoxyflurane.—Following a study of the pharmacology of a series of fluorinated hydrocarbons [Van Poznak & Artusio (39)] and a series of fluorinated ethers (40), methoxyflurane ($CH_3OCF_2CCl_2H$) was selected for initial clinical trial. A report on the first 100 cases was presented by Artusio *et al.* (41). Although methoxyflurane boils at 104.6°C., it is sufficiently potent so that anesthesia is readily induced when the concentrations of the agent in the oxygen stream are of the order of 2 to 3 per cent. Higher concentrations are difficult to obtain, which contributes a safety factor not noted in other volatile anesthetics. It is nonexplosive and nonflammable in practical concentrations at operating room temperatures. It is described as a complete anesthetic with profound muscular relaxation. Minimal secretory and nauseant effects were obtained. Sensitization to epinephrine was not notable and the major drawback, if any, was the slow recovery, undoubtedly due to remarkable fat deposition of the anesthetic (see (122)). Shortly afterward, Wasmuth *et al.* (42) reported favorably on 206 cases of anesthesia with methoxyflurane. They also noted an increase in blood sugar. Because of its

nonflammable character and the stability of the anesthetic state it produces, Van Poznak, Ray, & Artusio (43) have found it particularly useful for neurological surgery. The tendency to lower the blood pressure is probably positively useful in such work. All observers have remarked the cutaneous pallor of unexplained origin in the recovery period. Generally, they have found the drug most useful added to nitrous oxide-oxygen.

Although earlier observations suggested that it was not possible to sensitize the heart to epinephrine with methoxyflurane, Bamforth *et al.* (44) found that by using a standardized technique of infusing epinephrine in dogs they could readily produce atrioventricular block and concluded that methoxyflurane was similar to chloroform but not as potent as cyclopropane in sensitizing the heart to epinephrine. Dobkin & Israel (45) found the arrhythmias provoked by an epinephrine challenge during methoxyflurane anesthesia in dogs were less severe than those seen in similar experiments with trichloroethylene, cyclopropane or halothane, but were similar to those seen with halothane-ether azeotrope or light chloroform. Perphenazine was more effective than hydroxyzine in reducing the arrhythmias, but neither drug abolished them.

Dobkin & Fedoruk (46) have compared methoxyflurane and halothane in cross-over experiments in dogs. Hypotension and decreased cardiac output were greater with halothane than with methoxyflurane. Methoxyflurane had a more profound depressant effect on pulmonary ventilation. "Clinical choice between these two agents may be as difficult as that between chloroform and halothane."

It is possible to emulsify methoxyflurane and to administer the emulsion intravenously in man [Krantz *et al.* (47)]. The anesthesia so produced permitted surgery. One of the four subjects developed an urticarial rash, apparently due to the lecithin in the emulsifier.

Halothane.—Since its introduction in 1955, this compound, $CF_3CBrClH$, occasioned more than 500 papers and no little controversy. This latter essentially revolves about the question of safety in the hands of the general user. There seems to be no doubt that with proper equipment and experience, the expert can produce most excellent results; but that the inexpert can get deeply into trouble very quickly is also true. One of its earliest proponents, Johnstone, has reviewed the first 5 years and concludes "its advantages over other inhalational agents are so obvious that it seems reasonable to expect that its defects will not be appreciated until a better drug is discovered" (48). A summary of the characteristics of halothane was presented in "New and Non-official Drugs" (49). The concentration of halothane used in this country has constantly declined until presently concentrations of the order of 0.5 per cent to 0.8 per cent are most commonly employed [Smith & Volpitto (50)]. Johnstone, however, has concentrations as high as 10 per cent available (51).

The agent is administered by a variety of means varying from open drop for ophthalmic examination of ambulatory children [Schwartz (52)] to the closed circuit technique. This latter technique has gained increasing popu-

larity because of the high cost of the drug and increasing experience with the more precise devices for metering it into the gas stream. A number of papers have appeared recently showing that it may be used successfully with rebreathing techniques [Marrett (53), Gusterson (54), Robson *et al.* (55), Romagnoli *et al.* (56), Evans & Hutter (57), Hampton & Flickinger (58)]. Galloon (59, 60) has especially discussed the factors to be considered which control the concentration of halothane under these circumstances. The closed circuit concentrations of halothane and other anesthetics are reported by Fabian *et al.* (61). Certainly, for the less experienced anesthetist the use of an open technique is probably still to be recommended. [Anon., *Lancet*, I, 322(1961)].

General evaluations of halothane have been presented by Abajian *et al.* (62), Carson *et al.* (63), Costello (64) and Apivor (65). Swiss reaction is presented in a symposium just published (66). In general, these reports are favorable and the major precautionary statements revolve about the speed with which difficulties develop.

Gilbert *et al.* (67), Bayuk & Chen (68), Schettini *et al.* (69) and Deacon (70) have described the special use of halothane in neurosurgery. Nova (71), Cutter & King (72), and Sheridan & Robson (73) have found it useful in obstetrics because of the very low incidence of vomiting, particularly when light anesthesia is maintained to prevent uterine inertia.

Open cardiac operations are well carried out under halothane anesthesia according to Dawson *et al.* (74), Bull *et al.* (75), Zauder *et al.* (76), Taylor & Stoelting (77), and Stirling *et al.* (78). Its use with compressed air for cardiac catheterization studies is described by Norton & Kubota (79) as particularly satisfactory.

Excellent results in the changing of multiple burn dressings are described by Visser & Tarrow (80), anesthesia for bronchoscopy in children by Brown (81) and in dental surgery by Goldman (82), to mention a few specialized uses of this versatile anesthetic.

The special pharmacology of halothane has been a subject of considerable study. Duncan & Raventós (83) have explored the distribution and absorption of halothane in mice. It is evidently not metabolized. The general pharmacology of halothane in man was reviewed by D'Arcy *et al.* (84). They especially note inhibition of the contractility of the uterus and Marshall *et al.* (85) have noted depression of gastrointestinal motility.

The liver develops a transient fatty change but the kidney is little affected in the mouse, according to Gibson (86). When halothane is administered to dogs under somewhat hypoxic conditions, it has no adverse effect on liver fat, glycogen, and cellular structure. This situation ought to augment its toxicity, according to Haley & Wyant (87). However, fatal acute hepatonephritis was attributed to halothane by Vourc'h *et al.* (88). In sufficient concentrations halothane has a significant, reversible action on renal activity, according to Blackmore *et al.* (89) but these changes apppear to be functional rather than parenchymatous tissue damage.

According to Dobkin (90), there are essentially no changes of importance

in the acid-base balance during halothane anesthesia, attributable to a specific effect of halothane. A similar study was made by Holmdahl & Payne (91), but we have not seen it in detail. According to Nunn & Matthews (92), the oxygen consumption was depressed to 83 per cent of the basal value, a level comparable with natural sleep, and there is thus no indication that halothane specifically causes a reduction of metabolic rate.

The influence of halothane on the heart has been a matter of considerable discussion and apart from the catastrophes reported by Baxter (93) as the result of a defective instrument, it is generally agreed that arrhythmias may occur and may be exaggerated by sympathomimetic drugs (Johnstone & Nisbet (94)]. According to Muir *et al.* (95) they are quite frequent in cats. Bloodwell *et al.* (96) found that concentrations of 1.5 per cent produce considerable depression of myocardial contractility but that this was not necessarily deleterious in man.

It is generally observed that a fall in blood pressure occurs during halothane anesthesia [Black *et al.* (97), Cullen (98), Beaton (99), Dundee & Black (100)]. Advantage is actually taken of this effect to produce a degree of hypotension to suit the situation by Murtagh (101) and compared to cyclopropane, halothane anesthesia during hemorrhagic hypovolemia is highly satisfactory, according to Smith *et al.* (102). The exact cause of the hypotension has been a matter of discussion and initially it was thought to be due to sympathetic blockade but Millar & Morris (103) indicate that depression of sympathetic activity cannot be assumed to occur during surgical anesthesia with halothane. Using the exaggerated sympathetic response that Jamaican patients developed during surgery which results in a rise of blood sugar, Keating *et al.* (104) likewise concluded halothane does not block the sympathetic responses. A similar conclusion was reached by Enderby (105) and, as a result of extensive pharmacological studies, Burn & Epstein (106) have concluded that it is a direct effect upon the smooth muscle of the vessels of the spleen and of the intestine which acounts for the major part of the fall in blood pressure. Naturally, a certain amount of myocardial depression must occur with all anesthetics and, in the presence of this decreased peripheral resistance, could be expected to produce quite a drop. However, Moyers & Pittinger (107) have concluded that there really is not a statistically significant difference between halothane in their hands and other anesthetics with respect to this phenomenon. Actually, Payne *et al.* (108) observed a slight increase in cardiac output.

Comparative studies.—Bamforth *et al.* (109) have compared chloroform and halothane by blind study technique in clinical anesthesia. In a series of 100 patients anesthetized with chloroform and halothane as a supplement to nitrous oxide-oxygen anesthesia, and with the anesthesiologist not knowing which drug he was using, they found it was not possible to identify the agent solely by means of its clinical effect. Chloroform and halothane were compared in dogs using a crossover experimental plan and precision metering devices for the anesthetics. From this detailed study, Dobkin, Harland &

Fedoruk (110) concluded halothane is usually the better choice. The same authors (111) compared similarly halothane and trichloroethylene. Most notable was the increase of blood pressure under trichloroethylene. In other respects, there seems to have been little difference. The comparison of methoxyflurane and halothane in dogs by Dobkin & Fedoruk (46) has been mentioned above. In clinical anesthesia, Dixon & Matheson (112) found chloroform to be 10 times as potent as ether, and halothane 4 times as potent as ether, while trichloroethylene was less potent than ether.

Comparing the cardiovascular effects, Long, Pittinger, & Hamilton (113) found that isolated rabbit hearts were depressed by halothane, chloroform, ether and cyclopropane but that both halothane and chloroform increased, while the others decreased, coronary flow. Both halothane and chloroform depressed the work output and efficiency of the isolated spontaneously beating heart (Nayler, 114). Neither halothane nor chloroform had any effect upon the oxygen dissociation curve of human blood (Smith, 115). Boniface, Brown, & Kronen (116) using a strain-gauge arch preparation in the dog, found that ether, vinyl ether and cyclopropane produced approximately equal depressions of heart contractile force while chloroform was consistently more depressant. There was not a clear correlation between myocardial depression and systemic blood pressure. Robertson, Swan & Whitteridge (117 A) have shown ether, chloroform and trichloroethylene activate baroceptors and this effect is significant in controlling blood pressure (117 B).

Halothane produced no greater depression of hepatic function than cyclopropane or ether, according to Little, Barbour & Given (117). According to Jones, Margolis & Stephen, chloroform was the most toxic to the liver of mice, ether the least toxic and divinyl ether caused frank necrosis. Halothane produced fatty infiltration but no necrosis (118). Green *et al.* (119) compared chloroform, ether and halothane on the liver of dogs and found that chloroform produced changes in structure and function which were generally more severe than those produced by halothane or ether. Liver function in dogs after anesthesia with trichloroethylene and chloroform was compared by Richards & Bachman (120) who found that under their conditions chloroform produced a definite adverse effect on liver function while trichloroethylene did not. Liver impairment was found to be no greater after halothane anesthesia than after ether anesthesia; however, chloroform produced considerable dye retention in the studies of Virtue *et al.* (121).

Chenoweth *et al.* (122) anesthetized dogs with ether, chloroform, halothane and methoxyflurane and analyzed both arterial and venous concentrations by means of infrared spectrophotometry. The order of potency based on arterial blood levels converted to millimolar was halothane > methoxyflurane > chloroform > ether. As might be expected, arterial blood levels reflect the clinical state of the animal most accurately.

The content of methoxyflurane in the fat rose slowly and fell much more slowly than was the case with the other three agents. Tissue concentrations

were determined and the only spectacular finding was the discovery that the adrenal gland contained very much higher concentrations of all anesthetics than other vital tissues. Halothane was particularly noteworthy in this respect. Stewart & Stolman (123) have collected all the literature on analysis of body content of volatile anesthetics as well as solvents.

Chloroform, trichloroethylene, and ethyl chloride were compared with respect to their effect upon gaseous metabolism in rats by Hattori (124). Ether and cyclopropane were also studied. The respiratory responses of man were compared by Dundee & Dripps (125) who found that diethyl ether increases respiratory minute volume while trichloroethylene and trifluorovinyl ether produced tachypnea leading to inadequate ventilation. The blood sugar during halothane anesthesia was reported by Hunter (126) to remain unchanged while ether and cyclopropane greatly increased the blood sugar level. On the other hand, Chatterjee *et al.* (127) found that halothane markedly increased the blood sugar levels of mice compared to other anesthetics. Sabawala & Dillon found halothane, chloroform and trichloroethylene to depress isolated diaphragm and human intercostal muscle in a manner which could not be antagonized by neostigmine, suggesting that the site of action of the volatile anesthetics in depressing muscular responses is the muscle membrane (128).

Despite the potentiation of the neuromuscular effects of curare by all four compounds, Watland, *et al.* (129) found that only anesthesia with ether depressed the response of the gastrocnemius muscle to electrical stimulation of the sciatic nerve. Cyclopropane and chloroform actually enhanced muscle contraction while halothane had no effect.

In the central nervous system, Davis *et al.* report that ether is the most potent agent depressing evoked potentials from the midbrain reticular activating system and thalamus, followed, in an order of potency, by chloroform, vinylether and trichloroethylene (130) [see (131) *re* halothane alone]. The spontaneous electrical activity of the neocortical and rhinencephalic structures of dogs were studied by Domino & Ueki (132) with various anesthetics. They found a high voltage hypersynchronous activity during planes 1 and 2 of stage III. With trichloroethylene, this activity spread even further throughout the brain.

Dobkin & Purkin compared the effect of perphenazine on epinephrine-induced cardiac arrhythmias in dogs under halothane and halothane-ether azeotrope (133). It was found that epinephrine was far more likely to cause fatal arrhythmias under 0.5 per cent halothane than under 1 per cent halothane-ether azeotrope. Perphenazine was effective in preventing death with halothane and in reducing the duration and severity of arrhythmias with both halothane and the azeotrope. A similar study was performed by Dobkin, Donaldson & Purkin (134) using cyclopropane, chloroform and trichloroethylene. It was found that ventricular fibrillation was less likely to occur when epinephrine was injected during anesthesia with 0.5 per cent chloroform than with 25 per cent cyclopropane, or with 1 per cent trichloro-

ethylene. Premedication with perphenazine caused a significant reduction in the severity and duration of the cardiac arrhythmias provoked by epinephrine, but it could not eliminate them under acceptable conditions [see also (45)].

Determination of concentrations of anesthetics are now being made by gas chromatography (135, 136).

Miscellaneous.—From their previous studies (39) Artusio & Van Poznak (137) selected gaseous 1,1,1,2-tetrafluoro-2-bromoethane, given the generic name of teflurane, for further clinical trial. Using a 25 per cent mixture in oxygen, excellent anesthesia was induced in 30 patients which was characterized by rapid recovery. Further exploration of this nonflammable, nonexplosive base stable gas is anticipated.

Van Poznak & Artusio (138) selected 1,1,2-trifluoro-2-bromoethylmethyl ether, given the generic name of roflurane, for further study. It was found to be much like methoxyflurane but somewhat faster in producing anesthesia and more rapid emergence was noted. More detailed reports of these studies are to be anticipated. It should be noted that there is a marked chemical similarity between halothane and the three agents studied by this group. One wonders what unknown physical chemical property has caused these four usable agents to emerge from the welter of useless halogenated materials so far studied. Pauling (139) has just suggested "crystal" formations with water molecules.

A different series of compounds was investigated by Burns *et al.* (140) which included some interesting fluorinated cyclobutenes and butanes. [Cyclobutane itself is not satisfactory clinically (141)]. Seven of 15 compounds showed definite anesthetic properties and 3 were studied further by Burn, Epstein & Goodford (142). Only CF_2CHClF was worthy of further study and it was found to produce serious arrhythmias and hypotension in dogs and cats and was not carried to clinical trial. An investigation of new fluorine compounds in anesthesia has been reported by Glover & Hodgson (143) but we have not seen this in detail.

In another study of fluorinated hydrocarbons, Fabian, Dewitt & Carnes (144) uncovered 3-chloro-1,1,2,2-tetrafluoropropane ($CHF_2CF_2CH_2Cl$). This compound was studied in dogs and later in 29 patients. Although it was nonflammable and provided excellent muscular relaxation at light planes of anesthesia, significant disadvantage was noted because of the production of cardiac arrhythmias on induction. The analogous 3-bromo compound is under study.

Cole (145) made a thorough study of ethyl chloride as a gaseous anesthetic and concluded that when carefully metered it had properties not unlike trichloroethylene. The advantages seem to be slight, for this seems to be the only report on the subject. Interestingly, fluorinated ethylenes are, like ethylene, incapable of sensitizing the myocardium (146) but none seems to have come to clinical trial.

Trifluoroethylvinyl ether does not quite meet the requirements of a

nonflammable material under all possible circumstances, which may account for the somewhat limited interest in it, despite its excellent anesthetic properties. In an attempt to improve upon the flammability limits, Krantz, Ling & Kozler (147) formed an azeotropic mixture with it and Genetron 113 (1,1,2-trifluoro-2,2,1-trichloroethane). The results were sufficiently interesting to warrant a single human trial. The flammability limits of the azeotrope are given as 6.2 per cent in dry oxygen for the lower limit. Earlier studies with the undiluted material were reported by Sadove, Balagot & Linde (148) who found alveolar gas levels of 3.2 to 8.2 volumes per cent resulted in blood levels of 17 to 38 mg/100 ml and produced satisfactory surgical anesthesia not very different from diethyl ether. Later, Gainza *et al.* (149) examined the compound in dogs in detail and noted several differences from diethyl ether including that assisted respiration very easily became controlled respiration and that hypotension occurred in several patients without warning. A neutral position was the result of the study by Dundee, Linde & Dripps (150) on 300 human anesthesias. The EEG patterns were studied by Brechner & Dornette (151) who found only six specific patterns compared to the seven previously noted with ether. It has been shown to be stable *in vivo* by Musser, Park & Krantz (152). Its use in dentistry is reported by Slater (153) but the ability to strike sparks from teeth [Bourne & Morton (154)] would seem to be a contraindication.

Hexafluorodiethyl ether was introduced by Krantz *et al.* (156) as an inhalant convulsant. Its use in psychiatry for production of convulsions is not germane.

When halothane is dissolved in diethyl ether in the proportion of 31.7 parts of ether to 68.3 parts of halothane it all distills at one temperature, 51.5°C. Such a phenomenon is known as azeotropism. Boivin, Hudon & Jacques (157) prepared such a mixture and found it to be an effective anesthetic (158). Pharmacologically, it is equivalent to administering halothane and diethyl ether simultaneously in this constant proportion and the same effect could be achieved with separate anesthesia machines. Brown has reported that in oxygen the lower limits of explosiveness are 7.25 per cent. It will not propagate flames in air and the liquid has no flash point (159). The physical chemistry of the mixture has been further studied by Hall, Norris & Downs (160). The mixture has been condemned by Raventós & Dee (161) as being less satisfactory clinically as well as explosive and by Johnstone, Evans & Murphy (162) as "illogical." On the other hand, Dobkin (163) believes it offers significant advantages over halothane alone and that the ether counteracts many of the disadvantageous effects of halothane. Comparison of the cardiovascular effects have been made by Dobkin, Harland & Fedoruk (164) and by Wyant *et al.* (165) and there is less depression of blood pressure and some slight desensitization to epinephrine not unlike that observed when ether is added to cyclopropane. Its use in pulmonary surgery is recommended by Dechene & Claude (166) because of the decrease in respiratory and ventilatory difficulties and permissible use of the

electric cautery. Explosiveness is not entirely eliminated and thus the mixture might be very similar to trifluoroethylvinyl ether.

Toxicological Aspects

Industrial uses of these compounds are enormous and ubiquitous and with such use has grown a vast toxicological literature. As indicated in the opening paragraphs of this review, the space allowed has limited the reference to literature appearing during the past five years. One should consult Patty (167), Browning (168), and von Oettingen (169) for background information and a comprehensive understanding of the complete toxicological aspects of these compounds.

Methyl chloride.—Most of the recent toxicological papers concerning methyl chloride deal with human poisonings. Five cases, one of which resulted in death, were reported by Noro & Pettersson (170). Besides the symptoms reported previously, the authors observed slight leukocytosis in two cases, and lowering of the S–T segment in the ECG. Deafness and delirium, with neurological changes of hypokinetic or ataxic character, were reported by Bongard & Ivanova (171). They also suggest that acute intoxications can be accompanied by disturbance of internal organs, especially the liver. Roche *et al.* (172) also found that the liver and kidneys were affected in acute cases of intoxication in animals and in fatal human cases. Klimková-Deutschová summarized the neurological picture from 100 cases of methyl chloride poisoning (173). Acute poisoning generally was revealed by a preponderance of vestibular and cerebellar brain stem signs, with marked disturbances of cortical dynamics and subcortical relationships. The chronic picture was one of pseudoneurasthenia, central encephalopathy, and polyneuritic and polyradicular peripheral symptoms.

Redford-Ellis & Gowenlock (174) have initiated studies on the uptake of methyl chloride by various tissues. Interesting preliminary results indicated that brain tissue shows a high uptake of the chemical, with the lipid component very active in uptake. However, oxygen consumption of brain homogenates was unchanged after several hours of exposure.

Methyl bromide.—Very few well-documented cases of methyl bromide poisoning have been reported recently. One excellent report by Rathus & Landy (175) details seven cases of poisoning which occurred accidentally during a large-scale fumigation. None was fatal; however, four of the individuals had not recovered completely. Blood bromide levels of from 13.5 to 40 mg/100 ml were found in these four patients upon admission to the hospital, while the three who recovered completely had bromide levels of 2.4 to 9.6 mg/100 ml. These authors recommend Conway's (*Microdiffusion Analysis and Volumetric Error*, 3rd Ed., Crosby Lockwood, Publ., London, 1950) micro-diffusion method for estimating blood bromide in methyl bromide poisoning. Colorimetric methods such as the gold chloride method are not accurate enough for levels below 10 mg/100 ml. Martorano (176) ascribed symptoms exhibited by workers involved in methyl bromide prepa-

ration to exposure to this chemical. However, a lack of confirmatory air and blood bromide analyses makes the positive diagnosis of methyl bromide poisoning less assuring. The importance of EEG in the diagnosis of methyl bromide poisoning was stressed by Roche *et al.* (177).

Bromochloromethane.—Torkelson, Oyen & Rowe (178) studied the toxicological effects of this fire-extinguishing agent in 5 species of animals. Rats were exposed in single doses to concentrations ranging from 600 to 80,000 ppm for periods of 0.1 to 7 hr. Deaths were due to prolonged anesthesia and delayed deaths in survivors were exceptional. The maximum concentration which did not cause observable injury was 7,500 ppm. Rats, rabbits, guinea pigs and mice were exposed 7 hr daily for 6 months to levels of 500 ppm with no effect except on female rats. Significant adverse effects were limited to increases in liver and kidney weights and reversible microscopic liver injury. No bromism was noted, though all species had slightly elevated blood bromide levels. The authors recommend a maximum allowable concentration of 400 ppm for repeated human exposures, with a timeweighted average concentration not to exceed 200 ppm.

Dichloromethane.—This is one of the least toxic of the short-chain chlorinated hydrocarbons. However, its low boiling point, 39.8°C., and high vapor pressure, 420 mm Hg at 25°C., allows rapid evaporation, so that a hazardous atmosphere can be created. Allen (179) briefly described the industrial hygiene required in the safe handling of this compound. It is quite nonflammable, but if it is brought into contact with incandescent metal or an open flame, phosgene and hydrogen chloride, the decomposition products common to many chlorinated hydrocarbons, may be formed. Geritsen & Buschmann (180) attributed 2 deaths of workers using paint removers in an unventilated room where a kerosene stove was burning to the decomposition products of dichloromethane. A Russian report (181) indicates that ascorbic acid concentration in a number of organs of the rat rises sharply after exposure to methylene chloride.

Chlorofluoromethane.—Chlorofluoromethanes have utility as propellants in cosmetics. Toxicity and cutaneous tolerance (182), as well as effects on the ciliary activity of the respiratory epithelium (183), have been studied.

Chloroform.—Chloroform is similar to many of the other short-chain chlorinated hydrocarbons in its general capability to cause liver damage. Brauer, Leong & Holloway (184) studied the early changes which take place in an isolated perfused rat liver preparation exposed to the vapors of chloroform. Exposure levels were used which *in vivo* are known to produce liver injury compatible with survival of a rat or dog. Changes such as decreased bile flow, increased glucose concentrations in the perfusate, increased tissue sodium space, and early histological changes similar to those seen *in vivo*, were observed. The authors concluded that a biochemical lesion, rather than a lesion due to the release of sympatholytic agents in the blood, initiates chloroform injury to the liver.

Other experiments carried out to determine the effect of chloroform upon

the liver revealed the following observations. The permeability of surviving cells in liver slices was increased when chloroform was added to the preparation [Opie (185)]. Amasio (186) found that the DPN level of chloroform poisoned rat liver was 25 to 30 per cent lower than in normal control liver. Gündisch & Feszt (187) injected chloroform subcutaneously in rats. Histochemical studies revealed an increase in alkaline and acid phosphatase and a decrease in lipase enzyme activities in the liver parenchyma during the necrotic process, and a reversal in activities during healing. The enzymic changes preceded the morphological lesions. The present state of knowledge regarding chloroform toxicity to the liver makes it difficult to assess the significance of these observations.

A further study on the effect of chloroform on the necrosis of renal tubules in the C3H strain of mice was carried out by Culliford & Hewitt (188). This unusual necrotic effect on the renal tubules of the male mouse is the basis for a method to determine androgenic activity of injected compounds [Hewitt (189)].

Acute poisonings of humans by chloroform seem to have been reduced to a minimum [Gaultier *et al.* (190)]. Challen *et al.* (191) describe the results of repeated human exposures to concentrations ranging from 77 to 327 ppm. Medical examination of workers revealed various complaints which could be correlated with chloroform exposure. Although liver damage was probable, it could not be detected in those workers who submitted to liver function tests. The authors recommended that the maximum allowable concentration for chronic exposure should not exceed 50 ppm. Since this publication, the American Conference of Governmental Industrial Hygienists has lowered the recommended maximum allowable concentration from 100 to 50 ppm. Work still in progress in our laboratories indicates that chloroform is more toxic to animals upon long term exposure than previously assumed, therefore this downward revision seems entirely justified.

In an attempt to find a protective agent against chloroform poisoning, DiMaggio (192) found that 4-methylesculetin (2 mg/100 g body weight, daily) had a mild protective action in chloroform poisoning of male rats. However, the liver was the only organ which was studied histologically.

Bromoform.—Bromoform was found to be effective in the *in vitro* dissolution of gallstones, therefore it was tested *in vivo* in humans (193). The authors suggest either direct introduction into the bile duct, or oral administration, since 50 per cent of that administered orally to human subjects passed through the biliary duct unchanged. Surprisingly, the authors reported no adverse effect on the mucous membrane, even by concentrated solutions. It should be pointed out that von Oettingen (169) lists three fatalities and many more cases of illness resulting from accidental overdosage of bromoform to children.

Carbon tetrachloride.—This compound has continued to be the object of frequent study during the past few years. Importance as a cause of poisonings has maintained an interest in understanding the mode of action and in

having means of assessing toxic injury. In addition, it has remained a much used tool in physiological research, particularly in relation to the liver.

A recent review by Lewis (194) summarizes the present understanding of poisoning in man. An appreciable number of cases still occur in industry (195 to 199) and in the home (198, 200, 201). Occasionally phosgene is implicated where decomposition has occurred (202).

In general, this recent experience agrees with earlier reports that seemingly mild exposures can produce serious poisoning (195, 196), that ethanol and other factors predispose (198, 201) and that industrial exposures must be kept at very low levels (10 ppm or less) to avoid minimal effects (197). Of interest here is the showing by Stewart *et al.* (203) that oral ethanol in rabbits led to higher concentrations of CCl_4 in the blood upon inhalation of the vapor. Exhalation of CCl_4 vapor has been shown in man after a controlled 3-hr exposure to 10 ppm (204).

Work has continued in the past few years using a variety of compounds as protective or therapeutic agents for CCl_4 poisonings in animals. Some of this work has been directed toward discovering an effective agent, while some has utilized the agent as a tool in studying the mechanism of action of CCl_4.

Methionine has been studied previously and was recently reported to have aided in the rapid improvement of 3 human cases (199). In rats injected with CCl_4, Kobayashi (205) reported that the administration of DL-methionine reduced the increased lipid content and decreased the glycogen content of the liver. Asagoe (206) reported that methionine prevented the increase in collagen content of the liver. Other sulfur-containing compounds which have been utilized for further study in animals because of their protective action are glutathione (207), methylthiouracil (208), sulfaguanidine (209) and thioctic acid (6,8-dithiocaprylic acid) (210 to 214). The last compound has received considerable study in Italy and has been reported to have shown favorable results as a therapeutic agent in other human liver diseases (210, 211).

Agents which stimulate the production of pyridine nucleotides, nicotinic acid and its precursor, DL-tryptophan, were found to protect rats from acutely lethal doses of CCl_4 by Gallagher and co-workers (215, 216). The authors postulate that the increased tissue levels of pyridine nucleotides maintain higher mitochondrial coenzyme levels and thus sustain respiratory activity during a critical period. 5-Hydroxytryptamine was also found by Fiore-Donati and co-workers (217, 218) to exert a protective effect against acute damage, perhaps through a sparing action on tryptophan.

Of the vitamins studied for their protective action against CCl_4 poisoning, B_{12} has received the most attention (219 to 224). Kasbekar and co-workers (219, 220) postulate that the protection by vitamin B_{12} in acute carbon tetrachloride poisoning is non-specific and may be due to an effect on mitochondrial integrity. When studied on a chronic basis, Vaisler and co-workers (221) found that it protected against the loss of liver glycogen and

loss of liver function. Japanese workers (225) have reported that vitamin *E* protects against the increase in 14, 16 and 18 carbon saturated fatty acids in the liver, exerting its influence as an antioxidant. Pantothenic acid has been reported (226) to accelerate the repair of necrotic areas of the liver after CCl_4 poisoning. It was found to have no effect on the increase of liver collagen produced during CCl_4 poisoning (227).

Protective and therapeutic action against CCl_4 damage in rats by isolated rat liver mitochondria has been reported by Laudahn & Lüders (228, 229, 230). The highest therapeutic effects were obtained using mitochondria with intact respiratory chain phosphorylation. Bovine liver mitochondria were also used and found to be somewhat less effective. Tanyol & Friedman (231) have more recently reported a cat liver preparation to be effective in reducing fatty infiltration in the livers of cats given CCl_4 intramuscularly. Hog and calf brain extracts have extended survival time of rabbits and guinea pigs poisoned with CCl_4 (232).

Other compounds which have been reported to have more or less protective action against CCl_4 poisoning are lipotropic agents (233), betaine (234), sodium lactate (235) and aminoacetonitrile [$NH_2 \cdot CH_2 \cdot C:N$] (236).

Determination of liver function after CCl_4 poisoning by the determination of enzyme, metal, and/or vitamin levels in the serum has received considerable attention during the past five years. Because many of these experiments were designed to study liver function, and CCl_4 was used only to cause liver damage, attention is drawn to those that seem most pertinent from the viewpoint of carbon tetrachloride toxicity.

Since Wroblewski and co-workers (237) demonstrated late in 1955 that serum transaminase levels rise significantly in rats after CCl_4 intoxication, many papers have appeared which demonstrate the usefulness of this and other serum enzyme determinations to detect liver injury due to CCl_4. The papers of Cornish and Block (238, 239, 240) demonstrate the sensitivity of this determination to exposures of low magnitude and also its advantages over some other enzyme determinations. Other studies (241 to 246) on serum transaminase levels after CCl_4 poisoning have also demonstrated its usefulness as a liver function test. Fleisher & Wakim (247) report that the serum glutamic oxalacetic transaminase can be divided into two enzymes (GOT I and GOT II) after CCl_4 poisoning of the dog.

Increase in serum levels of another enzyme, ornithine carbamyl transferase, may be more indicative than the transaminases of exclusive liver damage because the former is almost unique to the liver. Studies by Reichard (248) demonstrated the value of this determination after CCl_4 poisoning of dogs. Other enzymes which increased in the serum of various animals after CCl_4 poisoning are xanthine oxidase (238, 239, 249), lactic dehydrogenase, malic dehydrogenase (241); fumarase (250), alkaline and acid phosphatase (temporarily) (251), quinine oxidase (252), and arginase (253, 254). Esterase shows an initial rise but drops the second day after exposure (240). The generally accepted hypothesis has been that CCl_4 effects an increase of many

of these enzymes in the serum by causing damage to the liver cell wall, thereby releasing the enzyme to the serum. Studies have shown that esterase and xanthine oxidase (240), fumarase (250), alkaline and acid phosphatase (251) and arginase (254, 255) concentrations in the liver decrease initially after CCl_4 poisoning. However, glutamic oxalacetic transaminase was found to increase slightly in the liver (240). Other enzymes which showed a decrease in the liver but have not been reported as having increased in the serum are succinic dehydrogenase (250, 256, 257, 258), aminoxidase, procainesterase, coenzyme A (259) and aconitase (250). These may be inhibited rather than released to the serum. In contrast to those enzymes which increase in the serum, cholinesterase (260, 261) and serum esterase (262) show decreases after CCl_4 poisoning.

A relationship between serum iron levels and hepatocellular necrosis due to CCl_4 poisoning in dogs was reported by Reismann *et al.* (263). The authors of this review have also studied serum iron levels after repeated exposures of dogs to CCl_4. An increase was noted at the beginning of a week's exposure and a decrease as the exposure progressed. It is possible that this increase and decrease is related to the previously mentioned xanthine oxidase levels in the liver (264).

Larson & Morrill (265) found fairly good correlation between acute CCl_4 poisoning and increased bromsulfophthalien retention, an old standby for liver function determination. Plasma and liver vitamin B_{12} levels in rats were studied by Okuda and co-workers (266, 267) after CCl_4 injection. In rats containing normal liver vitamin B_{12} levels, plasma B_{12} levels increased and the liver level decreased. This was confirmed by Kato & Murakami (268).

Plasma amino acids were determined after CCl_4 poisoning in rats by Knauff & Windsheimer (269). Initially, levels of most of the amino acids except glutamic acid and arginine increased abruptly, giving a total amino N of 200 per cent of normal. By 48 hrs they had become varied and the total amino N had returned to normal. Analysis of plasma and liver proteins (270, 271, 272) after poisoning also failed to indicate that their measurement would be of real value for diagnosis. Mizunuma (273) reported that 0.3 and 0.6 ml/kg of CCl_4 injected subcutaneously into rabbits caused directly related increases in serum mucoprotein levels. However, Lin (274) reported a significant decrease in serum mucoprotein levels when rabbits were given 0.2 ml/kg of CCl_4. These results are certainly incompatible.

The fact that the liver is one of the primary target organs of CCl_4 poisoning has been known for years, but the mechanism of action has been the subject of considerable research only during the past few years. In the following paragraphs, the mechanism-of-action hypotheses of several different groups of workers will each be reduced to simple terms. At present, the state of knowledge of the over-all mechanism of action has not advanced far enough to allow one to fit each of these hypotheses into the total picture of carbon tetrachloride poisoning.

One of the early hypotheses was that of Christie & Judah (275). They

theorized that CCl_4 acted upon liver cells by penetrating the membrane and causing a progressive disruption of mitochondrial function which ended in death of the cell. This hypothesis is also supported by Frunder and co-workers (276 to 281) and many others. It was continued by Judah & Rees (282) as being plausible though the original was attacked on the grounds that the changes resulting from mitochondrial disruption were of a secondary nature. Calvert & Brody (283) had noted that ethylene diamine tetra-acetate provided some protection against these disturbances in mitochondrial function, and that these disturbances generally occurred about 20 hrs after an acutely administered dose, while fatty infiltration occurred much earlier. Therefore, some consider the mitochondrial dysfunction of secondary importance, especially regarding initial injury.

Working on the theory that the damage to the liver mitochondria after CCl_4 poisoning may primarily be caused by anoxia, Brody and co-workers (284, 285, 286) discovered that the toxic effects on the liver of the intact rat could be alleviated to varying degrees by preventing the release of agents from the sympathetic nervous system of the animal. Following study of adrenergic blocking agents, adrenalectomy and spinal transection, they proposed "that carbon tetrachloride does not act directly upon the liver parenchymal cells but rather that the effects usually observed are promulgated via an action upon the central nervous system, or more precisely the sympathetic outflow of the autonomic nervous system" (287). Some reports (288, 289) do not lend complete support to this hypothesis.

Because fatty infiltration of the cells of the liver precedes mitochondrial damage, Recknagel and co-workers (290, 291) studied these early changes in order to determine the primary biochemical lesion. They observed (292) that the maximum concentration of CCl_4 in the liver occurred approximately $1\frac{1}{2}$ hrs after ingestion, and that thereafter there occurred a steady decline in its concentration. Concomitant with this build-up to maximum concentration of the chemical in the liver, they found a rapid increase in liver triglycerides and pathological changes in the endoplasmic reticulum (293, 294). From this work, and the fact that simultaneous administration of Triton with CCl_4 prevented the increase of triglycerides in the serum (295), the group postulated that "the primary lesion responsible for the pathological accumulation of liver fat involves inhibition or destruction of a hepatic triglyceride-secreting mechanism" (296). Of interest to this hypothesis is the finding by Rossi (297) that there occurred an early impairment in the ability of the liver to activate fatty acids.

Rees and co-workers (298, 299, 300) have recently hypothesized "that carbon tetrachloride irreversibly damages a reaction that is nonessential in the short term for the survival of the cell, and that as one consequence of this primary injury there is a secondary disturbance, for example, the entry of sodium and water into the cell" (301). Studies of interest to this hypothesis have been conducted by Gallagher (302) and Thiers *et al.* (303).

Many more papers have been published during the past five years which

will contribute to the over-all understanding of the mode of action of CCl_4. These can be referred to only briefly.

Perfused livers of rats which had been injected with small amounts of CCl_4 were studied by Plaa & Hine (304). Dysfunction of the liver could be detected though the dose was so small that no histologically destructive changes could be detected. Several reports on the detoxification ability of the liver after poisoning with CCl_4 have appeared (305, 306, 307). Islami *et al.* (308) found no great difference between normal liver tissue after poisoning, and poisoned tissue which had been regenerated after partial hepatectomy. It was found by Post *et al.* (309) that the rate of regeneration of the liver after acute poisoning with CCl_4 decreases with age in the rat. Hankiss (310) reported that rats, treated with sufficient CCl_4 when young to cause annular hepatic cirrhosis attained a substantially greater size at ½ to 1 year than did controls. Tritiated thymidine was utilized by Leevy *et al.* to study the regeneration of the liver tissue in rats after poisoning (311).

Histochemical investigations of livers poisoned with CCl_4 include studies on enzyme levels of proliferating connective tissues (312), fatty infiltration and necrosis (313), electron micrography of cells (314), vascular and cellular changes (315), enzyme activity and oxygen consumption (316), fat deposition and enzyme activity (317, 318, 319) and the influence of high protein diets on necrosis (320). Smuckler *et al.* [*Biochem. Biophys. Res. Commun.*, 5, 270 (1960)] report severe depression of fibrinogen and albumin synthesis parelleling the earliest changes in the endoplasmic reticulum.

Though it has been known for many years that CCl_4 also affects the kidneys, very little work has been reported in this field during the past five years. Enzymic and morphological changes were noted in the kidney ½ to 2 hours after poisoning by König *et al.* (321). The authors reported that the damage induced by CCl_4 in the kidney is a primary toxic response and is not secondary to liver injury. Grassi and co-workers (322) studied the protective effects of several hormones, singly and in combination, against kidney damage evoked by CCl_4. Combinations were somewhat effective, particularly against tubular degeneration. Loyke and co-workers (323) reported that subcutaneous injections of CCl_4 reduce experimental renal hypertension in rats.

Kaltenbach (324) has studied the blood picture of mice and rats poisoned with CCl_4, while Wirtschafter & DeMeritt (325) reported on the reticuloendothelial response. Effects were noted in the mast cells and in their number after vapor exposure of rats to CCl_4 (326).

Studies have been made on animals to assess the effect of CCl_4 upon the induction of tumors (327, 328, 329). The compound would probably be classed as a carcinogen by some; though there were no reports that the compound by itself is capable of causing neoplasia. One report indicated that the prolonged administration of the compound inhibited tumor formation in intrasplenic ovarian grafts in the rat (330).

Ethyl chloride.—Only one recent paper (331) on ethyl chloride has come

to our attention. The abstract indicates that the chemical was liberally applied to the shaven thighs of white rats. Edema of subcutaneous tissue and effects upon muscle and nerve fibers were noted. Nervous tissue became normal 10 days after exposure ceased, coinciding with the reduction of the inflammatory reaction. Widespread clinical use attests to the relative innocuousness of cutaneous application.

Vinyl chloride.—Of the short-chain halogenated hydrocarbons utilized as monomers for polymerization, vinyl chloride is probably the most important. Several recent papers have helped to delineate the toxicological picture.

Danziger and co-workers (332) recently studied the effects of acute exposures to anesthetic concentrations of vinyl chloride after 2 accidental deaths in industry. Danziger (333) described the circumstances involved in these two cases. The pathological findings in both were cyanosis, conjuctival burns, congestion of internal organs, especially lungs and kidneys, and failure of the blood to clot. Since no vinyl chloride could be detected at autopsy 3 and 8 hr. after death, mice, rats, and guinea pigs were exposed to levels of 10 to 40 per cent vinyl chloride in air for periods of time up to 30 min. A concentration of 10 per cent produced injury in rats and mice, while 30 per cent caused death. Guinea pigs were less susceptible, 3 of 5 surviving at a concentration of 40 per cent for 30 min. The principal pathological changes noted were congestion in the lungs, liver and kidneys, pulmonary edema and hemorrhage, and failure of the blood to clot. These results tended to confirm the cause of death in the overexposure of humans.

The effects on rats, rabbits, guinea pigs and dogs, of repeated exposures to vinyl chloride were reported by Torkelson *et al.* (334). After exposing animals 7 hr per day, 5 days per week, for up to 6 months, to air concentrations of 500, 200, 100 and 50 ppm, it was only at the last concentration, 50 ppm, that all species were completely free of deleterious effects. At a concentration of 100 ppm, there was only a slight increase in the average weight of the rat livers. From these studies, the authors have recommended that the maximum allowable concentration for repeated exposures in the workroom be 100 ppm and that the timeweighted average for daily exposure should not exceed 50 ppm. From this work, the present recommended theshold limit of 500 ppm as set by the American Conference of Governmental Industrial Hygienists appears to be too high.

Dichloroethane.—There are two structural isomers of dichloroethane, 1,1- and 1,2-dichloroethane. The 1,2-dichloro compound, usually called ethylene dichloride, has been studied much more extensively than the 1,1-dichloro compound, which is sometimes called ethylidene chloride. The authors were unable to find reference within the last five years to any work which specifically named 1,1-dichloroethane as the subject compound. Several papers concerning 1,2-dichloroethane are cited. Where the authors of papers did not specify the isomers, the term dichloroethane will be used.

Loscalzo *et al.* (335) studied the effects of 1,2-dichloroethane upon the heart, arterial pressure and respiratory activity of rats which had received

the compound intramuscularly and in rabbits which had been acutely exposed by inhalation. The compound caused bradycardia, ST segment depression, atrioventricular and intraventricular conduction disturbances, cardiac excitability, and a progressive decrease in the blood pressure to death. However, respiratory activity was reported to be improved.

Slyusar (336) indicated that light narcosis in rats as a result of dichloroethane aerosol exposure for 4 hr caused a surprisingly large fall in serum and tissue acetylcholinesterase 16 to 18 hr later. Cholinesterase activity in the liver, heart and pylorus was lowered approximately 30 per cent, while the serum level was lowered 43 per cent. Danishevskiĭ (337) has reported that dichloroethane administered internally to rabbits lowers blood phosphatase levels 12 to 80 per cent. The ascorbic acid content of the organs of male rats after both acute and repeated exposures to dichloroethane was studied by Malinskaya and Yanovskaya (338). The ascorbic acid content of the liver was increased 80 per cent over controls after an acute exposure to 20 mg/l (5000 ppm) of the vapor in air, while moderate increases of ascorbic acid were reported in the spleen, brain, heart and intestines. After a month's repeated exposure to 0.6 mg/l (150 ppm), increases were detected only in the liver and brain. Decreases in cholinesterase and phosphatases due to liver injury could be expected from dichloroethane intoxication, but the reason for the increase in tissue ascorbic acid levels is speculative. Analyses for dichloroethane were made in tissues of rabbits after acute poisoning, presumably by the oral route. The gastrointestinal tract contained the greatest amount of that which was recovered, while the least was found in the liver. The material could be detected in cadavers 25 days after poisoning of the animals (339).

Several cases of acute poisoning by dichloroethane have appeared in the literature in the past few years. Two fatal cases due to accidental ingestion, one a man of 79 and the other a child of 2, were reported by Weiss (340). In both cases, the outstanding symptoms developed in the central nervous system. There was also erosion in the gastrointestinal tract and toxic parenchymatous lesions of the liver and kidney, but these were unaccompanied by a clinical hepatorenal syndrome. Menschick (341) listed 27 cases of poisoning by inhalation of 1,2-dichloroethane previously recorded in the literature and described in detail 4 more which he observed in painters. Two were intoxicated to the point of semiconsciousness, while the other two were less severely affected. The author reported a hepatorenal syndrome in all four cases, with renal injury being transient. He suggests that this compound should be included in the "very dangerous substances" list, it being 70 per cent more toxic to animals than CCl_4 (acutely). Two other papers have appeared in the literature reporting acute poisonings by dichloroethane. Two cases were reported by Morozov (342) and a fatal case caused by a fumigant containing 70 per cent 1,2-dichloroethane and 30 per cent CCl_4 has been reported (343).

It is of interest to compare recommended levels of repeated exposure of humans to dichloroethane in Russia and the United States. In Russia,

Borisova (344) recommended a maximum allowable concentration of dichloroethane in air of 4 mg/m³ (~1 ppm). Her findings indicated that concentrations of 6 mg/m³ and up cause increasing vasoconstriction, decreasing light-sensation of the eyes, and reflex changes in rate, depth and rhythm of respiration. The average olfactory threshold was reported to be 23.2 mg/m³ (~6 ppm). In the United States, the maximum allowable concentration as recommended by the American Conference of Governmental Industrial Hygienists is 100 ppm (~400 mg/m³).

Dibromoethane.—Dibromoethane is commonly referred to as ethylene dibromide. Olmstead (345) has thoroughly described a fatal case involving the oral consumption of 1,2-dibromoethane, complicated by the fact that the patient had taken alcohol in excess for several years. Focal necrosis in the proximal tubules of the kidney, previously unreported in acute oral studies in animals, was noted. The effect of dibromoethane on the pituitary gonadotropic hormone of hens was studied by Olomucki (346). Feeds containing even small amounts of the chemical decreased egg sizes markedly and eventually resulted in complete cessation of laying. Egg size could be increased again by injecting follicle-stimulating hormone. The author believes that the chemical inhibits the formation or release of the hormone from the pituitary.

1,1,1-Trichloroethane.—The industrial importance of this solvent has increased tremendously the past few years. Torkelson *et al.* (347) have reported on the results of repeated exposures of animals to varying vapor concentrations of 1,1,1-trichloroethane. Rats, guinea pigs, rabbits and monkeys were unaffected after six months of repeated seven-hour exposures five days per week to 500 ppm. Male rats tolerated exposure of 0.5 hr per day to 10,000 ppm with no organic injury. The primary effect of the vapors of this solvent at high concentrations was anesthesia, with only a slight capacity to cause reversible injury to the lungs and liver. The authors also conducted ingestion, eye contact and skin contact studies. Results indicated no unusual hazards of handling in ordinary industrial operations. Human subjects, acutely exposed to 1,1,1-trichloroethane, reported light-headedness at 900 to 1000 ppm.

Stewart *et al.* (348) carried out controlled exposures of human subjects to 1,1,1-trichloroethane vapor concentrations of approximately 500 and 1000 ppm. The chemical in the post-exposure expired air was determined quantitatively by infrared spectroscopy. It could be detected in the expired air of individuals 20 hr after a 3-hr exposure to 955 ppm. The concentration of the chemical in the expired air was related to the level of exposure when exposures were of equal duration.

The metabolism of 1,1,1-trichloroethane in the rat after an intraperitoneal injection of the carbon-14 labeled compound was studied by Hake *et al.* (349). Approximately 98 per cent of the compound was recovered in the expired air as unchanged 1,1,1-trichloroethane. One half per cent of the dose appeared as carbon dioxide, while the majority of the remainder appeared in the urine as the glucuronide of 2,2,2-trichloroethanol.

Torkelson *et al.* (347) indicated knowledge of two fatal cases of over-

exposure to 1,1,1-trichloroethane, and another has been brought to the attention of the authors. Each of these fatalities was due to an anesthetic death resulting from over-exposure to the chemical in a tank or reactor.

Trichloroethylene.—Several reviews on the toxicology of trichloroethylene have appeared in the literature since 1955. A review by Grisler & Gallina (350) appeared in Italian in 1956. Bradoděj & Vyskocil (351) published a most comprehensive review the same year. Others which have appeared more recently are those by Williams (352), Edson (353), and Haas (354).

The studies of Baker (355) have verified the earlier findings which indicated that trichloroethylene adversely affects the central nervous system. Although no neuropathological changes could be detected in dogs after death from single acute exposures, repeated acute exposures caused scattered degenerative neuronal changes, while chronic exposures appeared to destroy selectively the Purkinje cells of the cerebellum. The conditioned reflex method of determining abnormal nervous responses in cats was used by Khorvat & Formanek (356). Four animals were studied during repeated exposures to trichloroethylene at a concentration of 0.4 mg/l (75 ppm) in the atmosphere. Their results suggested that disturbances occurred in the dynamics of cortical activity at this level of exposure. Grandjean (357) reported that exposure of rats to higher concentrations, 200 to 800 ppm for 3 hrs, did not modify the conditioned responses or the response time of animals. He found an increased excitability at these higher levels. It has also been reported (358) that human subjects exposed to low levels of trichloroethylene vapor show signs of nonspecific damage to nervous processes. These workers also found correlated decreases between blood levels of cholesterol and ascorbic acid in some cases.

Several papers have been published on the health of workers exposed to trichloroethylene in industrial operations. Usually the levels of trichloroethylene, trichloroethanol and/or trichloroacetic acid excreted in the urine were measured during these studies. Vague symptoms but no organic defects were reported by Hickish *et al.* (359) in a study of an operation where atmospheric concentrations of trichloroethylene varied from 62 to 637 ppm. Similar vague symptoms were reported by Mazza & Cascini (360). Several cases of human exposure were reported by Abrahamsen (379, 380).

A thorough review of the 384 cases of suggested trichloroethylene poisoning in Sweden during the decade 1941–50 was published by Andersson (364). Again, the symptoms were often vague, but intensity of symptoms could usually be correlated with degree of exposure. She reported that changes in liver function in rabbits were difficult to obtain at the low levels of exposure comparable to the reported industrial exposures. This has been confirmed in humans (365, 366), even after chronic exposures to polluted atmospheres. Increased urobilin excretion appeared to be the most significant of the many liver function tests (367). Serum transaminases were generally found to be normal (368). A report of deleterious effects on blood coagulation in workers exposed to trichloroethylene was published by Guyotjeannin & Guyotjean-

nin (369). Reinl (370) ascribed a case of scleroderma to trichloroethylene exposure in industry. Other papers reporting either chronic or acute industrial exposures have been noted (371 to 375). It is generally agreed that acute exposures result in anesthesia, with little aftereffect. Repeated exposures to low levels cause vague nervous symptoms and insignificant liver damage. There seems to be considerable disagreement as to the significance of these vauge symptoms, and therefore there is disagreement as to the maximum allowable concentrations to which a worker can be repeatedly exposed without deleterious effect.

The metabolism and metabolic products of trichloroethylene have received considerable attention. Souček & Vlachová (376, 377, 378) have published several papers on the excretion and analysis of trichloroethylene metabolites in human urine. Rubino and co-workers (361, 362, 363), in a series of papers, thoroughly studied the fate of absorbed trichloroethylene in workers.

It has been reported (362) that 30 per cent of that absorbed from an acute exposure was exhaled unchanged in about an hour. In humans, 73 per cent of that retained was identified in the excreted urine as monochloroacetic acid, trichloroacetic acid, and trichloroethanol (or its glucuronide) (376). The ratio of these metabolites in urine over an extended period of time was reported to be about 1:5:12. The monochloroacetic acid was excreted most rapidly, while trichloroethanol and trichloroacetic acid could be detected 14 days after a 5-hr exposure to 0.85 mg/l (157 ppm). Urinary excretion of metabolites was increased with simultaneous administration of glucose and insulin. Urinary levels of trichloroacetic acid or trichloroethanol have been used as indexes of exposure levels. In Czechoslovakia, Bardoděj & Krivucová (381) suggested levels, 160 mg/l for trichloroacetic acid and 320 mg/l for trichloroethanol, as the maximum urinary levels which would be attained by workers breathing trichloroethylene at an atmospheric concentration not greater than 0.4 mg/l (75 ppm).

A somewhat greater percentage of a dose was converted to trichloroethanol and less was converted to trichloroacetic acid in rabbits than in human beings (382). Intravenous glucose and ethanol increased the conversion of trichloroethylene to trichloroethanol in rabbits, while sodium lactate and fructose decreased the trichloroethanol excretion somewhat (383).

The enzyme system responsible for the oxidation of chloral hydrate, an intermediate in trichloroethylene metabolism, to trichloroacetic acid, and the subsequent reduction to trichloroethanol, has been studied by Cooper & Friedman (384 to 387). The system was purified 30-fold from rabbit liver, chloral hydrate being the only substrate utilized of the several aldehydes tested. In the reduction step, DPN-dependent alcohol dehydrogenase was found to be the principal mediator. Evidently, there is an excess of alcohol dehydrogenase in the body, since Lob (388) could find in both himself and in rabbits no difference in alcohol blood levels when it was consumed with and without trichloroethylene.

Several workers have very ably pin-pointed the chemical which caused severe hypoplasia in cattle fed soybean oil meal which had been extracted with trichloroethylene. Initial studies by Seto & Schultze (389, 390, 391) indicated that the bovine was able to metabolize trichloroethylene to trichloroacetic acid and trichloroethanol in a manner similar to other animals. They were unsuccessful in isolating the causative compound from soybean oil meal, using calves for bioassay (392). It was also found that trichloroethylene-extracted meat scraps caused similar deleterious effects in cattle (393). In 1959, both Schultze and co-workers (394), and McKinney and co-workers (395), synthesized the addition product of trichloroethylene and cysteine, *S*-(dichlorovinyl)-L-cysteine, and produced the same aplastic anemia in calves associated with feeding the trichloroethylene-extracted soybean oil meal. The primary mechanism of the toxic effect of *S*-(dichlorovinyl)-L-cysteine was studied by Mizuno *et al.* (396). It was found that the primary lesion was not due to an interference with DNA synthesis in leucocytes or leucopoietic tissue.

Chickens also succumbed to aplastic anemia when fed a diet containing 73 per cent trichloroethylene-extracted soybean oil meal (397). In addition, these chickens developed atrophy of the testes and marked depression of secondary male sexual characteristics.

Tetrachloroethane.—Tetrachloroethane has long been recognized as one of the most toxic of the chlorinated hydrocarbons. Workers exposed to tetrachloroethane were examined by Jeney and co-workers (398) who report finding rather vague complaints and symptoms in a rather large percentage of workers, plus enlarged livers in over one-third. Concentrations of the chemical ranged up to 0.08 mg/l ($\sim$12 ppm) in the atmosphere. The authors exposed rats and rabbits repeatedly for 8 weeks, 50 to 70 min daily, to 100 times this concentration and obtained deleterious effects, especially in the liver. Methionine and/or choline in the diet did not confer protection. In the group of workers studied by Paparopoli & Cali (399), liver enlargement, renal impairment, and myocardial effects were noted. Although carbon tetrachloride and dichloroethane were also present in the materials handled, the authors ascribed the poisoning mainly to tetrachloroethane.

Tetrachloroethylene.—Lob (400) considered the toxic effects of tetrachloroethylene to be little different from those of trichloroethylene. He reported detailed histories of 10 cases of alleged tetrachloroethylene poisoning. Baba *et al.* (401), in a study of serum from patients treated with tetrachloroethylene as an anthelmintic, found that albumin was decreased and α and β-globulins and urobilinogen were increased. These changes were ascribed to the hepatic functional disturbances caused by the anthelmintic.

Stewart *et al.* (402) exposed volunteers to controlled atmospheres containing either 100 or 200 ppm of tetrachloroethylene for up to 3 hrs. The compound could be detected in the blood of the subjects during exposure and was measured in the expired air for up to 100 hrs after exposure. The authors found a relationship between the concentrations of this compound in the

expired air after an exposure and the intensity of the exposure. Transient elevation of the urinary urobilinogen was noted in 2 of the subjects exposed to the higher concentration for 3 hrs. The authors recommend that vapor exposures of workmen to tetrachloroethylene should never exceed 200 ppm due to the onset of light-headedness and possible liver damage at higher levels. In the same paper, an accidental overexposure to approximately 395 ppm for 210 min was described. The concentration of the chemical in the expired air was followed for several weeks, and concentrations found were considerably above those reported for a timeweighted average exposure to 200 ppm for the same length of time. Again, tests for urinary urobilinogen were positive while other liver function tests were negative.

Tetrafluoroethylene.—Rats, rabbits, cats and mice were exposed to 0.5 to 10 volume per cent of this compound in air for 2 hr. The deleterious effects reported were hyperemia, especially of the brain, hemorrhages, emphysema and atelectases in lungs, hemorrhages in the spleen, dystrophic changes in the kidneys, desquamation of bronchial epithelium and disturbances of coordination. For rats and rabbits the lethal concentration of tetrafluoroethylene in the air for 2 hr was 2.5 and 4.0 volume per cent, respectively [Zhemerdei (403)].

Hexachloroethane.—Work by Lienert (404) showed that liver flukes were still susceptible to hexachloroethane given orally when the flukes were implanted subcutaneously in the rat. They concluded that the compound is present in the blood in sufficient concentration to cause death to the fluke, and therefore the efficiency of the drug is not due to its secretion in the bile. Jondorf, Parke & Williams (405) studied the metabolism of carbon-14 labeled hexachloroethane in rabbits. Tri- and dichloroethanol, the three chlorinated acetic acids, and oxalic acid were all detected in small amounts in the urine, which in three days contained 5 per cent of the radioactivity of the dose. Fourteen to 24 per cent of the dose was excreted in the expired air as carbon dioxide, tetrachloroethylene, tetrachloroethane and unchanged hexachloroethane. There was no trichloroethylene or monochloroacetic acid detected in the expired air or urine.

Halogenated three-carbon hydrocarbons.—A significant contribution to the detoxification of the *n*-propyl halides was made by Grenby & Young (406). *n*-Propylmercapturic acid was identified by paper chromatography in the urine of rats, rabbits, guinea pigs and mice which had been dosed subcutaneously with 1-bromopropane or 1-iodopropane. 1-Chloropropane was similarly metabolized by the rat and rabbit, but not by guinea pigs and mice. Synthetic *n*-propylmercapturic acid was converted into *S*-(*n*-propyl)-L-cysteine by incubation with extracts of rat liver or kidney.

The chronic vapor toxicity of allyl chloride (3-chloro-1-propene) to laboratory animals was studied by Torkelson *et al.* (407). Severe liver and kidney injury resulted when animals were exposed to 8 ppm (0.025 mg/l), 7 hr a day for 28 exposures. In an experiment at 3 ppm (0.009 mg/l), rats, rabbits, guinea pigs and dogs were exposed 127 to 134 times for 7 hr a day,

5 days a week. The only deleterious effect noted which could be attributed to the chemical was a reversible central lobular degeneration found in the livers of the female rats. The authors recommend that the allyl chloride concentration in the air of the working room should be kept below 2 ppm with a timeweighted average concentration for all exposures not exceeding 1 ppm. Safety precautions for industrial handling are also given.

In a study of several longer-chain halogenated hydrocarbons, Garkavi (408) found that tetrachloropropane, after three subcutaneous injections in the rat, caused a loss of weight, an increase in liver weight and solid residue of the liver, and a decrease in glycogen content of the liver. The action of tetrachloropropane was more similar to that of CCl_4 than was the action of either tetrachloropentane or tetrachloroheptane.

Halogenated four-carbon hydrocarbons.—1-Bromobutane metabolism in the rat and rabbit was studied by Bray & James (409). In their preliminary report, they noted that three compounds containing sulfur were excreted in the urine. One metabolite, after hydrolysis, yielded glutamic acid, glycine and *S*-butyl-L-cysteine, while the second yielded the latter two compounds. The third metabolite was identified as *n*-butylmercapturic acid. It appears therefore that 1-bromobutane is metabolized by the addition of cysteine or its derivatives to butane, with the splitting out of HBr.

Chronic administration of 1,3-dichloro-2-butene [$Cl\text{-}CH_2\text{-}CH{:}CCl\text{-}CH_3$] in the pig caused a disturbance in carbohydrate metabolism and changes in the morphological composition of the peripheral blood [Mkheyan (410)]. Mirzabekyan & Nikogosyan (411) report that 2-chloro-1,3-butadiene or chloroprene [$CH_2{:}CCl\text{-}CH{:}CH_2$] decreases the vitamin C content in blood and urine of dogs, and also lowers this vitamin in the liver, kidney, adrenals, spleen, and heart of guinea pigs and rabbits. However, it is difficult to correlate a vitamin C deficiency with toxic manifestations of exposure of humans to chloroprene as reported by von Oettingen (169).

Octafluorocyclobutane toxicity studies were reported by Clayton *et al.* (412). The study was designed to demonstrate the safety of this gas in food products. Acute and repeated exposures of rats, mice, rabbits, and dogs to unusually high levels of the compound caused no deleterious effects of significance. The studies were rather extensive and it was concluded that the compound is a safe propellant for food products.

Pattison (413) has recently published a monograph which includes toxicological data on halogenated hydrocarbon compounds in which at least one of the halogens is fluorine.

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