VINETHENE: RECENT LABORATORY AND CLINICAL EVALUATION *

STEVENS J. MARTIN AND E. A. ROVENSTINE

New York City

ALTHOUGH divinyl ether was apparently first prepared in 1887 by Semmler (1), its clinical application as an anesthetic agent was suggested only ten years ago. Leake and Chen (2) predicted that a compound combining the marked anesthetic power and relatively low toxicity of diethyl ether and ethylene would make a useful anesthetic agent. The significance of such an academic consideration involving the relationship of chemical structures and pharmacological action has been emphasized not only by the many laboratory publications which have since appeared but also by the clinical reports from many countries. It is estimated from the literature that the number of patients who have received Vinethene anesthesia exceeds a quarter of a million.

In 1934, the Council on Pharmacy and Chemistry of the American Medical Association published a preliminary report on Vinyl-ether-Merck deferring final consideration until more data had accumulated and until the product was marketed by the firm (3). In August 1937, "The Council voted to accept Vinethene-Merck for a period of one year for use as an anesthetic agent in short procedures and to publish this report at the time of acceptance" (4). No further official action has been taken. Because of the obvious clinical interest and the many publications since the last report of the Council, it is desirable to evaluate again the pharmacology and clinical application of this anesthetic agent. The literature reviewed covers the years since 1936, and is divided for convenience into those of laboratory and clinical nature.

LABORATORY STUDIES

General

Vinethene (CH_2–CH–O–CH–CH_2), the Council accepted name for Vinyl-Ether Merck, divinyl oxide, divinyl ether or Vinethene, possesses the following general characteristics (4). It is a highly volatile colorless liquid (boiling at 28–31 C.) with a slight purple fluorescence and a characteristic sweetish ethereal odor. It is inflammable and deteriorates on exposure. Its preparation for anesthesia contains 3.5 per cent. absolute alcohol and 0.01 per cent of phenyl-alpha-napthylamine to prevent freezing on evaporation, polymerization and decomposition.

* From the Division of Surgery, Department of Anesthesia, New York University College of Medicine and the Division of Anesthesia, Bellevue Hospital.

Ruigh, et al, who successfully synthesized pure divinyl ether in 1931, were unable to confirm Semmler's report that Vinethene may be prepared by treating divinyl sulfide with dry silver oxide (5). Semmler's original product was never analyzed and was characterized by a boiling point of 39 C. and a molecular weight of 71. Synthesized Vinethene has a boiling point of 28.3 C. and a molecular weight of 70.

The rate of elimination of divinyl ether was studied by Ruigh in the anesthetized dog and compared with that of ether and cyclopropane (6). He has shown that while the initial rate of elimination of divinyl ether is much greater than that of ether, later it is slower and finally is less than that of ethyl ether. Cyclopropane behaves like divinyl ether. The quick initial rate of elimination corresponds to the period of early recovery of consciousness. It is believed that the final rate of elimination is determined chiefly, in the case of agents with a high oil-water partition coefficient such as divinyl ether and cyclopropane, by the slow rate of diffusion of the substance from the fat depot in the body. Inasmuch as such fat has a poor blood supply it serves as a reservoir for the drug. The author cautions against prolonged administration of lipotropic agents such as Vinethene and cyclopropane especially if the continued presence of residual anesthetic agents in the body is undesirable for the patient.

Peoples (7) studied the effects of Vinethene and ethyl ether on the oxygen consumption of albino rats kept in a closed chamber at a constant temperature but with a varying concentration of one or the other anesthetic agents. Anesthesia was continued for forty to ninety minutes at one of two levels—either light or deep, the level determined by the muscle twitchings, respiratory rate and reflexes. It is pointed out that in light Vinethene and diethyl ether anesthesia, there is an increase in oxygen uptake probably due to increased muscle tone or activity of the respiratory muscles. In deep Vinethene anesthesia, there is a reduction in oxygen utilization to values considered normal for natural sleep. In deep ether anesthesia, however, the fall in the oxygen uptake is even greater than can be accounted for by a decrease in muscular tone alone. Such a decrease occurs notwithstanding adequate oxygenation and perhaps indicates a critical depth of anesthesia below which an abrupt fall of oxygen utilization follows. This may signify that a sudden change occurs in the intrinsic metabolism of most of the body cells. While the rats were presumably at the same level of deep anesthesia with each agent, the author fails to point out whether a critical decrease of oxygen utilization in deep Vinethene anesthesia can occur at all. The clinical significance of such a finding is not clarified. One might imply from the author's data that a critical decrease in oxygen utilization may not occur in deep clinical Vinethene anesthesia.

The chemical effects of soda lime on Vinethene, ether and cyclopropane during the use of the carbon dioxide absorbers for anesthesia were recently reported by Adriani and Rovenstine (8). It was shown that

there was neither a chemical change in these agents during the clinical use of soda lime nor any reduction in the efficiency of the soda lime due to these agents. Vinethene is thus quite stable when used with the carbon dioxide absorbing technics.

In another investigation, Adriani studied the stability of fifty different samples of Vinethene, exposing them to conditions which are encountered clinically and under certain experimental conditions such as repeated opening and closing of the containers and changes in temperature (4–32°), humidity (0–100 per cent) and luminosity of light (9). The purity of Vinethene was investigated by the accepted qualitative tests (reducing substances) of the Council on Pharmacy and Chemistry of the American Medical Association. In addition, tests for oxidizing substances, acetaldehyde, residue and pH, were determined. The potency of the agent subjected to the various conditions was determined clinically in eighteen samples. It was concluded, on the basis of absence of impurities and pH changes, that Vinethene is free from deterioration for seven to ten days when containers are opened, and then closed and kept under the ranges of temperature and humidity of the operating room. In three samples, tests were made nine months after the expiration date on the bottle. It would seem that the manufacturers were unduly cautious regarding both the expiration date and in their statements regarding stability after Vinethene had been opened.

The recent interest in the autonomic effects of various anesthetic agents has prompted Adriani and Rovenstine (10) to study the effect of Vinethene and other agents on the activity of cholinesterase. Determining the freed CO_2 from serum bicarbonate as an index of the rate of hydrolysis, they concluded that Vinethene does not inhibit cholinesterase in the hydrolysis of acetylcholine. Because of the structural similarity of Vinethene to diethyl ether, whose sympathetic stimulation is well known, such a finding is to be expected. In another report (11), it was shown that Vinethene produces relaxation of the bronchial musculature by sympathetic stimulation. A similar effect is produced by ethyl ether except that it is accomplished by direct action on the musculature as well as by sympathetic stimulation.

Lott, Smith and Christiansen (12) reported that the preparation of Vinethene can be accomplished in homogeneous reaction mixtures by the withdrawal of hydrogen chloride from beta beta-dichlorethyl ether with the use of either potassium hydroxide or sodium alcoholates. However, these alkaline reagents must be dissolved in alcohols which do not participate in etherification of the Williamson reaction type.

Emerson, et al (13) studying the side-effects of ether and Vinethene anesthesia on rats and rabbits, emphasize again the rough correlation between the effects of ether and of epinephrine and add that ketonemia and some hyperglycemia can be obtained with Vinethene if there is prolonged light anesthesia without premedication. Nevertheless, while Vinethene produced less hyperglycemia, the ketosis was marked al-

though the average for the latter was below that reached in a rabbit given epinephrine. The deliberately prolonged second stage of anesthesia in these experiments was offered as a possible explanation of these findings. In the light of Knoefel's theory (14) that many of the side-effects of ether anesthesia are sympathetic in character and due to the liberation of adrenalin, it appears that Vinethene is less sympathomimetic than ether. Continuing this study, Emerson later (15) found that Vinethene anesthesia for thirty minutes in unpremedicated cats showed no diminution in the adrenalin content of the adrenal glands, whereas following ether anesthesia, a significant decrease was noted. It was pointed out that such a difference was not due to the different type of induction anesthesia with the two agents but essentially in variations in the physiological side-effects of ether and Vinethene during surgical anesthesia. Again one might conclude that Vinethene apparently exerts considerably less sympathetic stimulation than ether. In this connection, it is interesting to note that Vinethene does not significantly affect cardiac automaticity in the prepared dog and that the blood pressure gradually decreased with increased depth of anesthesia (16).

The acute safety of ether, Vinethene and chloroform in the production of the "obstetric degree" of analgesia was studied in dogs by Draper and Whitehead (17). The margin of safety was calculated from a relationship between the minimal dose for arrest of respiration (MDRA) and minimal dose for analgesia (MDA) and expressed as percentage. It was concluded that Vinethene was intermediate in position between chloroform and ether with respect to the margin of safety and potency. Chloroform possessed the highest potency and the least margin of safety and the reverse was true in the case of ether. It is emphasized that the margin of safety alone is an inadequate guide to the probable clinical mortality. Accordingly, the authors studied the success of resuscitations from overdoses of Vinethene, ether and chloroform in dogs. Resuscitation was uniformly successful in all instances when an overdose of Vinethene or ether was given and failed in 13 per cent (6 cases) following chloroform. While they also conclude that Vinethene is the least satisfactory of the three agents used for smoothness of analgesia, the authors refrain from making any single choice for obstetric analgesia and point out that their aim has been "to make our method conform, as far as possible, to the established principles of biological assays." In a subsequent study (18), Draper and Whitehead suggest the calculation of a "safety index" for these anesthetic agents based on the probability of overdose and the probability of failure to resuscitate. According to their findings, the safety index for Vinethene, ether and chloroform is 100, 96 and 9.5, respectively. Their approach to the problem might be questioned and the authors admit that they "do not have sufficient data as yet from which to derive a satisfactory index for divinyl ether." However, they believe it obvious that it is in the order of ether rather than chloroform.

Vinethene may be isolated from human brain, liver and lung by a micromethod suggested by Domanski (19). In his in-vitro experiment, this author found that the average recovery from 500 Gm. of tissue containing 0.16 to 0.39 cc. of Vinethene is 58.2 per cent but from aqueous solution it is about 90.5 per cent. The method appears satisfactory but no clinical application is mentioned.

Gastro-intestinal Tract.—Using six dogs with Thiry-Vella loops of the upper jejunum, Burstein (20) showed that contrary to in-vitro results, Vinethene, like ether anesthesia, produced diminished muscular tone and complete inhibition of intestinal contractions in all planes of surgical anesthesia. Meek and his associates (16) not only confirmed these findings but added that there is also an absence of propulsive activity. Further, it is demonstrated that gastric tonus increased slightly during surgical anesthesia but gastric contractions were inhibited. They state that "rise in gastric tonus was anticipated in view of the spontaneous flow of vomitus frequently observed during surgical anesthesia and often beginning fifteen to twenty minutes after induction." The clinical significance of this observation on animals is of no small import to the anesthetist. However, in view of clinical literature reported herein, this statement may be challenged. The emptying time of the stomach in dogs under Vinethene anesthesia (21) determined by repeated fluoroscopic examination was prolonged only 7 per cent above the control values as compared to 7, 15, 40 and 64 per cent for cyclopropane, nitrous oxide, ether and chloroform, respectively. No studies are available concerning the effect of Vinethene anesthesia on the motor activity of the colon or on the secretory activity of the gastro-intestinal tract.

Liver.—The effect of Vinethene anesthesia on the liver has received further attention since the early studies on this subject (22–23). Goldschmidt et al (24) studied liver damage after the administration of chloroform, ether and Vinethene to dogs with a Gwathmey three chamber volatilizer on a normal and a high carbohydrate diet. They concluded on the basis of histological evidence that Vinethene like chloroform anesthesia, resulted in liver necrosis which could be largely prevented by admixing the anesthetic agent with oxygen. Further, a high carbohydrate diet was as effective as oxygen in protecting the dog's liver against necrosis due to chloroform and more so against that due to Vinethene.

More recently, the Wisconsin investigators (16) studied the histological effects of Vinethene anesthesia on the liver in rats and dogs and confirm, in part, some of the previous findings. They agree with Molitor that in the rat Vinethene produces no liver damage presumably because of the marked power of regeneration of the liver in this species. They confirm the work of Goldschmidt (24) that in the dog, "there is a minimal duration of Vinethene anesthesia necessary to elicit liver damage." This quotation is based on evidence obtained from thirty minute daily

anesthetizations of dogs for seven days. However, they add that "central zonal necrosis can be produced routinely" by Vinethene anesthesia and that such "an effect is not due to anoxemia in their studies." By comparison with chloroform as well as with ether, Vinethene appears to these authors to be more toxic in producing central zonal necrosis of the liver in dogs. In this phase of their studies, 4 dogs were anesthetized for one hour, once a week for three weeks with the aid of an endotracheal airway and the carbon dioxide absorption apparatus and pure oxygen as a diluent for the Vinethene. To eliminate further the possibility that liver changes were due to anoxemia, determinations of blood oxygen were made. The occurrence of moderate to severe liver damage despite the use of 88 per cent oxygen during Vinethene anesthesias does not support Goldschmidt's contention that oxygen greatly alleviates such liver changes. No mention is made of the diet which was provided the animals used in these experiments. While it is unfortunate that such careful histological studies were not completed with functional tests of the liver, these findings have clinical significance.

Cardiovascular System.—Continuing his studies on cardiac automaticity, Meek et al (16) report that Vinethene has no significant stimulating effect on the automatic tissues of the dog's heart as measured by the occurrence of arrhythmias following injections of adrenalin, neosynephrin and cobefrin. It is more similar in this respect to diethyl ether than to chloroform or cyclopropane. Relatively few arrhythmias occurred such as extrasystoles, A–V rhythm, A–V block, ventricular extrasystoles and ventricular tachycardia. S–A acceleration with the accompanying electrocardiographic changes is the most characteristic effect of Vinethene anesthesia on the heart not previously sensitized with adrenalin. Very little is said about blood pressure except that it is decreased with increasing the depth of anesthesia. No studies have been made on cardiac output, venous pressure or blood flow.

Central Nervous System and Spinal Cord.—The so-called running movements previously noted by Goldschmidt (22) and Waters (25) have been seen in 108 surgical Vinethene anesthesias in 46 dogs (16). The aberrant muscular movements of the four extremities were eliminated in all cases only when anesthesia progressed to complete intercostal paralysis. They were never noted in over 400 anesthesias with diethyl ether, cyclopropane or chloroform. Meek and his associates attempted to localize the region of the dog's central nervous system stimulating such movements and concluded that it is below the level of the corpora quadrigemina and most likely in the spinal cord itself. Morphine-scopolamine premedication prevents such movements in most cases.

Kidney.—The effect of Vinethene anesthesia on renal function (16) was studied by determining changes in urea clearance tests in 4 dogs anesthetized for sixty minutes each week. A comparison was then made with the results found in dogs anesthetized with chloroform for one hour per week for seven weeks. It was found that Vinethene anes-

thesia resulted in a progressive decrease in kidney function up to the point of complete anuria. Following weekly chloroform anesthesia, as in the case of cyclopropane and diethyl ether, no change in kidney function occurred.

This survey of the investigations published since 1937 reveals that research concerning Vinethene has not been extensive. In comparison to the great number of clinical studies published during this period interest by research workers is more surprising. Among the laboratory publications completed, fortunately, significant findings have been reported.

Confirmations of data already published have been accompanied by new facts and have served to establish the limits within which Vinethene may be safely employed and to obviate attempts to make this agent accomplish a task for which it is ill-fitted.

CLINICAL EVALUATION

Vinethene has received considerable clinical attention during the past four years. Well over one hundred publications have appeared from many domestic and foreign institutions dealing with a variety of subjects. These studies have been arbitrarily divided into the following categories.

General.—A review of the literature during this period reveals that Vinethene anesthesia was administered in more than 35,800 cases. To this may be added the vast numbers of unreported anesthesias. The time of anesthesia ranged from less than a minute (26) to four and a half hours (27).

It is interesting to note that while Vinethene has now been used for many major cases and practically all types of minor surgery, it was employed for dental surgery in 49.7 per cent of the 35,800 cases noted. Cartin (28), Dawkins (29), Feldman (30, 31), Goldman (32) and others (33, 34, 35, 36, 37, 38, 39, 40, 41) have reported gratifying results in large series of Vinethene anesthesia for dentistry. Continuing the enthusiasm of Bourne (42, 43, 44), Ball (45), Elam (46, 47, 48), and others (36, 49, 50, 51) believe Vinethene to be very satisfactory for obstetrical patients.

Vinethene has also been suggested in thoracic surgery (52) and used in patients with pulmonary tuberculosis because there is relatively slight irritation to the lung (53, 54) and the anesthetic agent permits adequate oxygenation and a rapid recovery of reflexes. Vinethene was not satisfactory in some cases, although no untoward results were observed (55). Despite the many major operations for which Vinethene anesthesia was used alone or as the primary agent, the literature reveals the fact that it is most commonly used for minor procedures or the ambulatory patient (56). It has recently been used with apparent success for such procedures by physicians in our Army (57) and Naval (58) hospitals and in England during present war conditions (59).

Age.—Age, per se, apparently is no contraindication to Vinethene anesthesia for it has been used successfully in patients ranging from one month (60) to 76 years of life (61). According to Cartin (28), Gross (60), Kohlmayer (62), and others (26, 29, 63, 64, 65, 66, 67) who have anesthetized well above 8000 children, Vinethene is an ideal anesthetic agent. Most of the procedures were minor and of short duration. Gross states that Vinethene "was extremely satisfactory for minor operative procedures and in no case was there any alarming or untoward reaction accompanying or following the anesthesia. The extremely rapid induction period with this drug permitted full muscular relaxation in thirty to forty-five seconds. The period of recovery was likewise short, and in practically all cases the patient had regained consciousness in two to three minutes and older children were talking and sitting up by the end of this time. There was postanesthetic vomiting in only 5 cases." However, there may be struggling during induction as compared to ethyl chloride and convulsions may occur (36, 64, 69).

Technics.—The administration of Vinethene has been performed by the open drop method, the closed inhaler (bag and mask), the semi-closed and the carbon dioxide absorption technic. The first technic is by far most commonly employed in this country, although during the last few years the absorption method has gained considerable support. This change has been due largely to the experimental studies which showed that the addition of O_2 to Vinethene anesthesia decreases liver damage (24, 27).

No outstanding advantage can be noted with any of the procedures suggested for the open drop method. They all fundamentally depend upon the rate of the falling drops, the number and size of the layers of gauze, and upon admixture with air. However, many technics have been suggested (70). It is claimed that children may be asleep after 15–20 drops have fallen while in strong adults it may take 100–150 drops per minute (71). Others make no mention of the number of drops per minute but simply emphasize the time of induction which may range from fifteen seconds to five minutes. Because of the high volatility and cost of the agent, this method obviously is uneconomic and prohibitive in prolonged cases (72, 73). Many have suggested the use of a new apparatus (74, 75) for the administration of Vinethene after induction by the open drop method or the use of a nasal catheter (76).

Our British confreres have popularized the closed inhaler method. The Clover or Goldman's (26, 32, 77) inhalers are most commonly employed, and are intended for single dose administrations lasting only a few minutes. Recently Kaye (72) has devised a sight-feed Vinethene apparatus which is not only portable but can be used for anesthesias of at least twenty minutes' duration. The apparatus can also be attached to a soda lime absorption machine. Jones (78) reports an improved method of Vinethene administration using a record syringe with a modification of the valves used in the Goldman apparatus.

Vinethene is also administered by the carbon dioxide absorption technic. Ball and Richards (45) use a Rowbotham's chloroform bottle attached to a Boyle's gas-oxygen apparatus. Harris (79) has devised a drip feed for Vinethene in the machine and claims to have obtained excellent results once the rate of drip has been adjusted. Mallinson (80) similarly has developed a drip feed which permits accurate measurement of Vinethene administered and can be attached to the Shipway machine. In this country Vinethene is being administered with all standard anesthetic apparatus. In the absorption technic Vinethene has been successfully given with oxygen (45, 81, 82, 83, 84) for long periods as a complement to nitrous oxide anesthesia (54, 85, 86, 87, 88, 89, 90), ethylene oxygen, avertin with amylene hydrate, spinal or intravenous evipal anesthesia (68), as an induction agent for ether or with 75 per cent concentration of ethyl ether and 25 per cent Vinethene (35, 44). Ravdin (83) advises the addition of oxygen whenever Vinethene is used for surgery exceeding thirty to forty-five minutes. This is considered as a safeguard against possible liver pathology. Bourne (44) first recommended the use of 25 per cent Vinethene and 75 per cent ether by both the open and closed methods stating that one obtains not only the rapid induction without the usual disadvantages of ethyl ether induction but also the decreased volatilization which occurs when Vinethene is used alone. The method is considered safe for the general practitioner and relatively inexpensive. Harris (35) and Cartwright (61) are similarly enthusiastic with this mixture although the latter author writes, "The Vinethene mixture is inferior to ether for operations requiring deep anesthesia, is more expensive than chloroform or ether and cannot be kept from day to day. It is highly inflammable and the odor is unpleasant to the anesthetist although not to the patient. It is possible, as illustrated by one case reported in this paper, that the heart may be affected by the mixture in a small proportion of cases."

Induction.—Induction of anesthesia with Vinethene by any of the above technics is admittedly rapid, and as in reports prior to 1937, it is regarded by many as one of the important clinical features of this agent. It is considered an ideal anesthetic for children and according to Baetzner (63) is far superior to ether and safer than chloroform or ethyl chloride (91, 92, 93). The earlier reports were exceptionally favorable. It is now pointed out that induction, despite the fact that with Vinethene it is considered as "smooth and non-irritant," may occasionally be complicated by salivation, nausea and vomiting, masseter spasm, cyanosis, laryngeal irritation, cough, excitement (62, 64, 68, 71, 83, 87, 94) and even muscular twitching and slight convulsive movements may occur (95). However, as pointed out recently by Livingstone (68) and Ravdin (83), complications during induction with Vinethene are decidedly infrequent as compared with other agents. Premedication with morphine, codeine, atropine or barbiturates have been suggested (61, 71, 83) for the more prolonged anesthesias. This is not always neces-

sary and as in the past, is not used for dental or ambulatory cases or various anesthesias for children (99). In the careful analytical study by Livingstone and her colleagues (68), while premedication does decrease the occurrence of marked mucus and slight to marked excitement, it does not eliminate such complications during induction.

Maintenance.—For short periods of anesthesia, maintenance generally presents no problems. For surgery exceeding twenty to thirty minutes some have noted particularly that Vinethene gives inadequate relaxation of the abdominal wall (96, 98). Others (40, 47, 68, 83, 86, 88, 100) claim that skeletal and abdominal muscle relaxation was satisfactory throughout the surgical procedures. This discrepancy may be explained in large measure by the difficulty in maintaining an even (60, 101) plane of anesthesia due to the marked volatility of Vinethene. As pointed out previously (4) respiratory signs are of greatest value in denoting the stage of anesthesia. In surgical anesthesia, respirations are quiet, full, regular and at a slightly increased rate (68). There is no significant change in pulse rate (33, 68).

Recovery from Anesthesia.—Recovery from Vinethene anesthesia, as in the case of induction, is very rapid and accompanied by a small incidence of complications. Nausea and vomiting were the complications most commonly noted but occasionally there were convulsive movements, cyanosis, moderate amount of mucus and a questionable urticaria on the day after anesthesia (68, 69, 102). Lyons (103) reported a burn on the cheek due to pressure of the thumb on Vinethene saturated gauze during a twenty minute Vinethene anesthesia. Consciousness returns quickly, a fact particularly appreciated by both the ambulatory patient and the office practitioner. A mild hyperglycemia comparable to that found with several other anesthetic agents is produced by Vinethene anesthesia (68). Except for the occurrence of convulsions which will be discussed below, the more recent findings noted in recovery from Vinethene anesthesia have merely served to emphasize those already reported prior to 1937.

Postanesthetic Course.—The postanesthetic course following short Vinethene anesthesia for dental surgery is negligible except that mentioned below (69). For other anesthesias, the following has been noted to occur one or two times each in a detailed analysis of 325 Vinethene anesthesias by Livingstone et al (68): post-operative fever, mild post-operative hemorrhage following tonsillectomy and adenoidectomy, cough, coryza, bronchopneumonia (after intratracheal anesthesia with Vinethene and ether) cyanosis, and convulsion one day postoperatively. All except the last noted complication were not unexpected with the physical condition of the patients in whom they occurred.

Convulsions.—Increasingly more attention has been paid to this complication of Vinethene anesthesia during the past four years. Convulsions have been noted during induction (95), maintenance (29, 69), and upon recovery (36, 68, 69, 102) from anesthesia given by either the open

drop method or the carbon dioxide absorption technic. Dawkins (69) has given much consideration to this subject and reports convulsions in 9 out of 2406 Vinethene anesthesias. In four instances, the convulsions appeared near the end of the operation under deep anesthesia by the CO_2 absorption technic. Each patient was induced with evipan, a fact of particular interest in that the author found no report of ether convulsions following premedication with a barbiturate. Convulsions in two cases were terminated by another evipan injection; in the others no medication was given and the convulsions ceased. One patient died ten days later from embolism although no evidence of damage from Vinethene was found at autopsy. In the other 5 cases, convulsions appeared in children upon recovery of consciousness from Vinethene given for dental extraction. Although all muscles were involved, consciousness was lost and respiration ceased, artificial respiration was promptly followed by recovery. However, these children exhibited peculiar reactions for a few hours subsequently, running about the room and banging their heads against the wall upon being disturbed, reactions which the author characterizes as a "syndrome." He states that "This 'syndrome' has now been accepted by the nursing staff as a normal complication of Vinethene anesthesia and no undue alarm is felt." Perhaps these aberrant muscular movements are similar to the running movements noted previously by Goldschmidt (22), Waters (25) and Meek (16) and represent central nervous system irritation.

Liver Damage.—The controversial matter of liver damage following Vinethene anesthesia in excess of an hour, apparently settled once by the studies of Ravdin et al (27, 83) and more recently open to question again by those of Meek (16) et al, is reflected in many clinical reports. Bourne (43) states that very slight liver damage may follow Vinethene anesthesia but as quoted from his experiments on the dog, this is most commonly due to cyanosis and anoxemia. In other studies on anesthesia for obstetrical patients, no liver damage was noted. Confirming his laboratory investigations with Goldschmidt (24), Ravdin (27) has repeatedly emphasized that the administration of oxygen with Vinethene for anesthesia exceeding forty-five minutes results in no liver necrosis in patients. It is admitted, however, that Vinethene is more toxic to the liver than ethyl ether but less so than chloroform. These findings are not in agreement with the recent studies reported by Meek et al (16) who showed that Vinethene anesthesia in the dog with adequate oxygenation results in central zonal necrosis of the liver.

That liver damage may occur unless due precaution and careful selection of cases are exercised is stressed by many anesthetists (85, 89, 95, 104, 105, 106, 107). In a series of 1000 Vinethene anesthesias, Dörffel states no injury to the liver has been noted. Kohlmayer (61), in his series exceeding a thousand Vinethene anesthesias, reports two deaths in which yellow atrophy of one liver was found. In the postoperative death reported by Light (93), liver damage was found although the

patient had received a large amount of ether and a small amount of Vinethene. Such deaths, in addition to those pointed out in the years preceding 1937, emphasize once again that Vinethene anesthesia is not without its disadvantages. The need for functional studies of the liver in patients anesthetized with Vinethene appears more urgent than ever to detect early and mild changes which are never visualized on the autopsy table.

Kidney Damage.—The investigation by Orth, Slocum, Stutzman and Meek (16) showing that Vinethene anesthesia in dogs produced a progressive decrease in kidney function as measured by urea clearance tests, presents a direct and immediate challenge to clinical anesthetists. It is hoped that reports will soon be forthcoming on the subject from many research minded anesthetists.

Explosions and Fires.—Despite the inflammability and explosiveness of Vinethene, no clinical report has been found describing such an accident. Such a possibility is fully appreciated and recently emphasized again (108, 109).

SUMMARY

A survey of the literature on Vinethene published since 1936 is reported in an attempt to determine the progress made by laboratory and clinical investigators in the evaluation of this relatively new anesthetic agent. Many significant experimental findings have been made, some of which are of great practical importance.

From the laboratory investigations it might be inferred that Vinethene does not merit consideration as a substitute for ether or cyclopropane and that it should not be used to produce profound anesthesia or for operations requiring more than a few minutes to complete. The significance of the conflicting reports on the serious question of liver and kidney damage should be investigated more completely especially in man. With the knowledge already available, hepatic or renal insufficiency should be considered a contraindication to the use of Vinethene.

From the clinical point of view, it appears that while age, per se, is no contraindication to the administration of Vinethene, it is more commonly employed for children. Its use for minor surgery and especially in dental procedures has become increasingly popular. Technics have increased in number but the open drop method is still most popular. For surgery exceeding thirty to forty-five minutes, the carbon dioxide absorption technic with oxygen as a diluent is advised. Despite certain characteristic properties of Vinethene, complications may occur during all stages of anesthesia. By comparison with other volatile drugs these appear small in number. However, attention should be directed to the increasing emphasis given by clinical reports to the occurrence of convulsions and liver damage associated with Vinethene anesthesia.

The clinical reports indicate that the use of Vinethene is increasing, that it is being found useful for surgical procedures of short duration

(less than twenty minutes) requiring little muscular relaxation and that it is most satisfactorily given by simple open technics. It may also be of value to complement less potent gases, such as nitrous oxide, for anesthesias of short duration or to induce ether anesthesia, although these have been less emphasized in published reports.

477 First Avenue.

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