

TCE-CNS

HAZARDS IN THE USE OF THE CLOSED-CIRCUIT TECHNIQUE FOR TRILENE ANAESTHESIA

BY
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Within the past two years trilene (trichloroethylene) has been increasingly used as a form of general anaesthesia. It has certain advantages over ether and cyclopropane, such as non-inflammability, and it is regarded as safer than chloroform, for there is much less risk of ventricular fibrillation. When diathermy is necessary, particularly in the region of the head and neck, trilene commends itself as a suitable non-explosive anaesthetic agent. As a rule I have limited my use of trilene to thyroid and breast operation cases. Its use in a closed-circuit machine appears to fall in line with what is almost a routine practice of most anaesthetists—that is, the carbon dioxide absorption technique for inhalational anaesthetics. There are many advantages of such a method, the outstanding one being that a quiet operation field is ensured by the diminished respiratory excursions. In cyclopropane anaesthesia this technique is of course essential for practical and economic considerations. The purpose of this paper is to show that it is dangerous to use trilene with a closed-circuit technique.

Illustrative Cases

Case 1.—Mrs. A., aged 67, a frail thin woman, was a poor risk for operation for stone in the hepatic duct. On Nov. 22, 1943, she was given premedication of omnopon gr. 1/6 and scopolamine gr. 1/300; then pentothal g. 0.5, followed by endotracheal cyclopropane. The operation lasted 1½ hours, during which she was given 750 c.cm. of plasma. No trilene was used in this case. The same apparatus, however, had been employed to administer trilene to a patient immediately preceding this one. In the evening following operation her temperature was 99° F. and she vomited repeatedly. This vomiting started 12 hours after operation and continued for three days, when she first complained of difficulty in swallowing and numbness over the face. She was seen by Dr. Wilfred Harris on Dec. 11, and I am indebted to him for the following neurological notes: "Slight diplopia in all directions. Left third nerve shows partial ptosis, and the left pupil is sluggish. There is bilateral slight weakness of both external recti, with homonymous diplopia. The voice is markedly nasal and there has been nasal regurgitation, and the right soft palate is obviously paretic. Fifth nerve:—There is total anaesthesia to pin-prick and even hand pressure over both first divisions, and the right second division, including the hard palate. The left second division is totally analgesic to pin-prick, but hand pressure is felt on the cheek. Moderate analgesia of third division on both sides, mostly on the right. Total motor palsy, with complete jaw-drop, is present. There is loss to taste over the right second division on the palate, but taste on both sides of tongue is fair."

This patient had to have a gastrostomy (under local anaesthesia) on Dec. 26 because of the inability to swallow. The gastrostomy tube was removed after five weeks (Jan. 31, 1944), and she is now swallowing food reasonably well. Although her general condition has vastly improved, the fifth and other nerve palsies show slight improvement only.

Case 2.—Miss B., aged 50; operation, Dec. 6, 1943—local excision of benign tumour of breast. Premedication: omnopon gr. 1/3, scopolamine gr. 1/150, pentothal g. 0.5 in bed were followed by a very short further induction with cyclopropane and by nitrous oxide, oxygen, and trilene, using the closed-circuit technique. The duration was only 20 minutes. About 12 hours after the operation vomiting started; this continued for 36 hours. On the evening of Dec. 7 the temperature was 99°, and lasted two days. In the early morning of Dec. 8 she complained of double vision, stiffness of the face, and difficulty in swallowing. Dr. Harris saw her on Dec. 11, and reported: "She has a bilateral third-nerve paresis, the right being practically complete. The right pupil is much dilated, with very little reaction to light or convergence. Fifth nerve:—She complains that the face feels hot and 'tingly' over both cheeks (second division). Nearly complete analgesia to pin-prick over first and second divisions of both sides, including conjunctivae, and upper gums and palate. No pain on pricking the inside of nostrils. No motor fifth-nerve weakness, the masseters and external pterygoids being strong. Little if any anaesthesia of the third division of fifth. Sense of smell good. She has no nasal regurgitation, the soft palate rises normally on phonation, and there is no analgesia of the pharynx; but there is a suggestion of slight palatal weakness, because she cannot blow out her cheeks properly." There has been only

very slight improvement in this patient eight weeks after the onset of the paralysis.

Both cases therefore showed well-marked bilateral trigeminal anaesthesia, oculomotor palsy, and also difficulty in swallowing, the latter symptom being more pronounced in Case 1.

In the first case the trigeminal paralysis was total for the upper two divisions, with a total motor fifth-nerve palsy. In this first case, too, the right half of the soft palate was completely paralysed (tenth cranial nerve), and though the oculomotor paralysis was less than in Case 2 there was additional weakness of both sixth nerves. Case 1 also showed scars of recent herpes on the right upper and lower lips, which strongly suggest that a "toxin" had affected the Gasserian ganglion. Dr. Harris pointed out that herpes frequently appears over the lips and nares after Gasserian alcohol injections.

Discussion

On making inquiries it was found that a case immediately preceding Case 1, on Nov. 22, had pentothal, nitrous oxide, oxygen, and trilene, via a closed-circuit machine, for the removal of an adenoma of the thyroid; this patient subsequently vomited a good deal and complained of giddiness. She was seen a few weeks later, but there was no evidence of her having had any paralysis. It is worth emphasizing that Case 1 did not have trilene, and it should be noted—an important fact—that the soda-lime canister was not changed between the cases. Case 1 would thus have been exposed to a prolonged inhalation of any toxic products that may have formed in the soda-lime canister when the trilene had been administered to the immediately previous case. The idea that a toxic product had formed in that canister was suggested by the fact that between the dates of the first case (Nov. 22) and the second (Dec. 6) eight others were given pentothal followed by cyclopropane anaesthesia with the same apparatus, and with no ensuing paralysis. It seemed an extraordinary coincidence that on the only two days that trilene was used a patient developed paralysis. Also it was noted that only recently at this hospital, for the convenience of dispensary ordering, a change-over had been made to another well-known brand of soda-lime (B). This appeared to give very good absorption clinically; but it was noticed that the canister became much hotter than with the previous brand, A (solfol soda-lime). Another point with Brand B was that when it was necessary to change the soda-lime it was often found to be caked, and sometimes had to be dug out of the canister; whereas Brand A could always be easily shaken out. This led to the conclusion that Brand B, though it gave very good absorption, was the more hygroscopic. Accordingly, a full investigation, and analyses, of the soda-lime, trilene, and cyclopropane were started, and Dr. H. E. Cox kindly undertook the chemical analyses. Results of analyses of the two brands were:

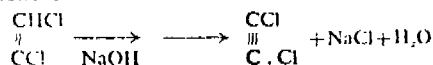
	A (Solfol)	B
Calcium hydroxide	84.1%	77.6%
Sodium hydroxide	1.2%	11.2%
Carbonate (calculated as Na ₂ CO ₃) ..	4.8%	5.4%
Moisture	7.4%	3.0%

Equal quantities of the two were then exposed in a moist atmosphere at room temperature, showing:

	A	B
Water absorbed after 18 hours ..	0.54%	2.23%
" " " 66 " ..	1.38%	6.77%

It will be observed that the clinical finding that Brand B has a greater avidity for water is confirmed. Also, it is particularly important to note that the caustic soda content of B is more than 9 times that of A. The significance of the latter point is discussed shortly. In his analysis Dr. Cox found no evidence of any deleterious substances in the cyclopropane or trilene; but experiment showed that, whereas when cyclopropane was passed through soda-lime no reaction occurred, with trilene through soda-lime a reaction took place, producing a distinctive sour smell. This reaction took place slowly at room temperature and rapidly at blood heat. As I have personally recorded temperatures of 110° F. using Brand A soda-lime and 178° F. when using Brand B in the canister of a circle absorber under conditions of anaesthesia, it will be readily understood that any chemical interaction will almost certainly be considerably speeded by this increased warmth. Trilene is itself very reactive, and is a derivative of acetylene, which chemically is one of the most reactive compounds

known. Dr. Cox also pointed out that trilene with soda-lime produces new and potentially toxic products, one of which is dichloroacetylene. This is easily oxidized to phosgene and carbon monoxide.



Trilene heated with alkali produces dichloroacetylene, and experiment shows a recognizable formation of this at even 98° F. If the heating is continued in the open, the dichloroacetylene, being very volatile, disappears, but if a condenser is used the dichloroacetylene accumulates and there is an explosion, producing phosgene. But when an excess of trilene vapour or an inert gas is maintained, dichloroacetylene does not further oxidize, and no explosion or phosgene formation occurs. This explains the fact that experimentally no phosgene reaction occurred in the circuit of the apparatus. The distinctive smell noted above is almost certainly due to the formation of dichloroacetylene, the physiological activity of which is at the present time unknown, and it is dismissed in all the literature as spontaneously explosive.

The fact that Brand B soda-lime is shown to contain more than nine times the amount of caustic soda, that it is more hygroscopic, and that it generates more heat under anaesthesia supports the clinical observation that this brand would definitely be more reactive towards trilene, with the production of toxic oxidation substances. This view is supported by the clinical evidence that no case of paralysis occurred while Brand A of soda-lime was used at the hospital; and no case occurred when employing my own apparatus for closed-circuit trilene anaesthesia, in which Brand A has always been used. The high temperature generated by Brand B soda-lime, and therefore of the inhaled anaesthetic gases, is of further disadvantage to the patient; it leads to excessive sweating and capillary engorgement (Hewer, 1942) even at 104° F.

Conclusion

The relatively low incidence of post-trilene paralysis is, according to the above facts, due to three factors:

1. Fortunately, the vast majority of administrations with this anaesthetic agent have been given in an open circuit. As there is no evidence of direct formation of oxidation products in the trilene without soda-lime, it seems that there is no apparent risk when trilene is used in an open circuit.
2. The high temperatures generated and recorded in the canister of a circle absorber during anaesthesia have been at the point of maximum intensity of reaction, usually after the soda-lime has been in use for about an hour. If the soda-lime has already been in use for some time we do not get these very high temperatures, which are an exciting factor in the oxidation of the trilene into toxic products.
3. The actual amount of caustic soda available for this chemical reaction with the trilene has been shown to be considerably higher in some brands of soda-lime. It appears to be the most important factor—apart from the rise in temperature—for this effect on the trilene.

McAuley (1943) describes three cases of bilateral trigeminal anaesthesia, and it is to be noted that in every case the closed-circuit technique had been used. Lengthy anaesthesia does not seem to be necessary for full toxic effect. In his cases the durations were 20 minutes, 30 minutes, and 1½ hours, and in one of my cases the anaesthesia lasted only 20 minutes.

Summary

Evidence is brought that trilene anaesthesia in a closed circuit is dangerous, and may result in trigeminal and other cranial-nerve palsies. The palsies are disabling and may be permanent.

This danger is shown to be due to toxic oxidation products formed by the interaction of soda-lime and trilene.

This reaction is speeded by the heat generated in the soda-lime.

The exact caustic soda content and hygroscopic properties are shown to vary in different brands. This, it is indicated, is an important factor in the occurrence of these cases.

My grateful thanks are due to Dr. H. E. Cox for his help in these investigations. I also wish to thank Mr. Lancelot Bromley for much encouragement and for many helpful discussions.

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INTELLIGENCE AND SEASON OF CONCEPTION

BY

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Many studies have shown that there is an association between season of birth, or of conception, and intelligence. Evidence has recently been ably marshalled by myself the contributor of the most substantial body of evidence. Children whose time of conception is centred on the months of May to October are on the average somewhat more intelligent than those conceived during the other half of the year. Analysing the results of the various investigations, it naturally shows a certain amount of difference in the results selected for contrast (with suitable reversal in the Northern Hemisphere): (1) birth months May to October, corresponding approximately to conception months August to January; (2) birth months November to April, corresponding approximately to conception months February to July. Children falling into these two groups will for conciseness be referred to in this paper as winter and summer children respectively.

The Alternative Explanations

Two explanations of the difference are possible: (1) season of conception influences intelligence; or, (2) season of intelligence influences season of conception. Now, it is a remarkable fact that, with one partial exception (see below), I am familiar with the literature, every investigator has assumed without discussion that the first explanation is the correct one. Some of the hypotheses advanced are: (a) the range of orthodox biological opinion—for example, "the higher metabolic level of parental protoplasm during winter cold seems to be transmitted through the placenta, and to exert a lasting effect upon the future of the offspring." There would seem to be nothing in this unlikely, however, in the assumption that the prenatal environment of the developing child is more favourable at one season as compared with another. This would be an addition to the list of known non-genetic prenatal influences, such, for example, as the well-known effect of maternal age in mongolism, or the effect of being a child in congenital pyloric stenosis (Cockayne and MacCallan, 1943).

The partial exception to this unanimity of opinion is provided by Huntington (1938). His observations on such highly gifted persons have led him to postulate a season of birth which is different from that indicated by the studies. He is concerned to explain the discrepancy, and (p. 325): "It seems highly probable that the three types mentioned—namely, the passionate, the unintelligent, the weak-willed—contribute more than their proportional share to the excess of births which still occurs at the height of the animal rhythm. We should expect many of the children of such parents to have low intelligence, and they may suffice to overbalance the unusually bright children born at the same season, thus giving a low average intelligence regard to his main thesis, however, he is convinced that the season which affects intelligence. Thus he states: "Our new knowledge as to season of birth can be of use only if we use it in one of two ways. First, we can discover the present seasonal distribution of births. Secondly, we can discover the exact conditions which make certain seasons favourable, and then take steps to create those conditions in other seasons."

Practical Importance of the Problem

Apart from the theoretical interest of the problem, the practical importance of deciding which explanation is right one is not inconsiderable. Many writers have argued to its logical conclusion and urge that knowledge of season of conception would aid in human betterment. Choose one example, Mills (1941) sums up as follows the findings reported in these pages have a very direct

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OCCUPATIONAL EXPOSURE OF OPERATING ROOM PERSONNEL TO TRICHLORETHYLENE

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INTRODUCTION

TRICHLORETHYLENE is unique among anaesthetic agents in that it is also used widely as an industrial solvent. As a result, chronic toxicity studies of TCE have been performed in greater amounts than for other anaesthetic agents. The threshold limit value for TCE has been set at 100 ppm.

In 1976, Stewart *et al.*¹ reported ten experimental human exposures to TCE, 100 and 200 ppm, for periods of one hour to a five-day work-week. The only troublesome response was a sensation of mild fatigue and sleepiness in five subjects during the fourth and fifth consecutive days of exposure to 200 ppm. Following single exposures of 200 ppm for one hour and 100 ppm for four hours, TCE was detectable in end-expired air of subjects for 44 and 38 hours, respectively.

A recent study by Salvini *et al.*² has demonstrated that 110 ppm TCE administered to volunteers for four-hour periods resulted in a significant decrease in performance of standard psychophysiological tests. These authors suggest that the recommended TLV appears very close to the concentration capable of interfering with psychophysiological efficiency, even in the absence of other undesirable subjective or objective manifestations.

In light of these findings, we determined the range of concentrations of TCE in the operating room during administration of TCE anaesthesia under usual working conditions, and measured end-expired breath levels of TCE in patients following TCE anaesthesia and in anaesthetists following administration of anaesthesia.

METHODS

Trichlorethylene anaesthesia was administered to six patients for periods ranging from 75-160 minutes using a non-rebreathing system with a Sierra valve. A total gas flow of 9 L/min was used. TCE was administered using a Vernitrol vaporizer, with concentrations ranging between 0.25 per cent and 1.0 per cent.

TCE concentrations were measured in parts per million, using a Beckman GC 72-5 gas chromatograph with a flame ionization detector. The limit of detection was 10 ppb.

Operating-room concentrations were determined in five separate areas of the operating room. Operating-room air was collected by slowly withdrawing samples into a large gas-tight syringe. Samples were injected into Saran bags and taken to

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TABLE I
CONCENTRATIONS OF TRICHLOROETHYLENE IN THE OPERATING ROOM

Location		PPM Trichlorethylene	
		30 min	60 min
Directly over valve [4']	Range	1-81(6)	1-103(5)
	Mean	25	30
One foot from valve [4']	Range	1-11(6)	1-9(5)
	Mean	3	4
Two feet from valve [4']	Range	0.2-1.4(6)	0.5-2.4(5)
	Mean	0.8	1.2
Foot of O.R. Table [5']	Range	0.5-1.4(6)	0.4-0.9(5)
	Mean	0.8	0.7
Corner of room [5']	Range	0.2-0.7(5)	0.2-0.8(5)
	Mean	0.5	0.6

Concentrations of TCE in various locations after 30 and 60 minutes of anaesthesia. Numbers in parentheses indicate number of samples in each group. Number in brackets indicate height above floor at which samples were taken. The two highest levels, 81 and 103 ppm, occurred during a case where the anaesthetist and anaesthetic machine were partially enclosed in a tent of surgical drapes.

the laboratory for analysis. Samples were taken directly above the expiratory valve, one foot, and two feet from the valve, all at levels four feet above the floor. In addition, samples were collected at the foot of the operating table, and in the far corner of the room away from the anaesthetists and five feet above the floor. Samples were collected at 30 and 60 minutes following induction of anaesthesia. The air turnover rate in the operating rooms was 12 times per hour.

The rates of excretion of TCE were determined in three patients and in three anaesthetists by measuring concentrations in end-expired air of subjects at intervals following exposure. Samples were collected in Saran bags. Subjects were instructed to inhale, exhale about two-thirds, and then breathe into the bag.

RESULTS

Operating room air concentrations of trichlorethylene ranged from 0.2 ppm in the periphery of the room to 103 ppm at a level of four feet directly over the expiratory valve. Average concentrations in each area measured are listed in Table I.

Three patients had detectable levels of TCE in end-expired air for 4, 11, and 12 days following TCE anaesthesia for 30, 100 and 160 minutes, respectively, as shown in Figure 1.

Three anaesthetists had detectable levels of TCE in end-expired air from 2 to 7 hours following termination of administration of routine clinical anaesthesia ranging from 60 to 150 minutes in duration (Figure 2).

DISCUSSION

The study by Salvini *et al.* raises the question of another possible occupational hazard in the operating-room environment. Does exposure to low levels of anaesthetic gases impair judgment and ability to react rapidly when the situation

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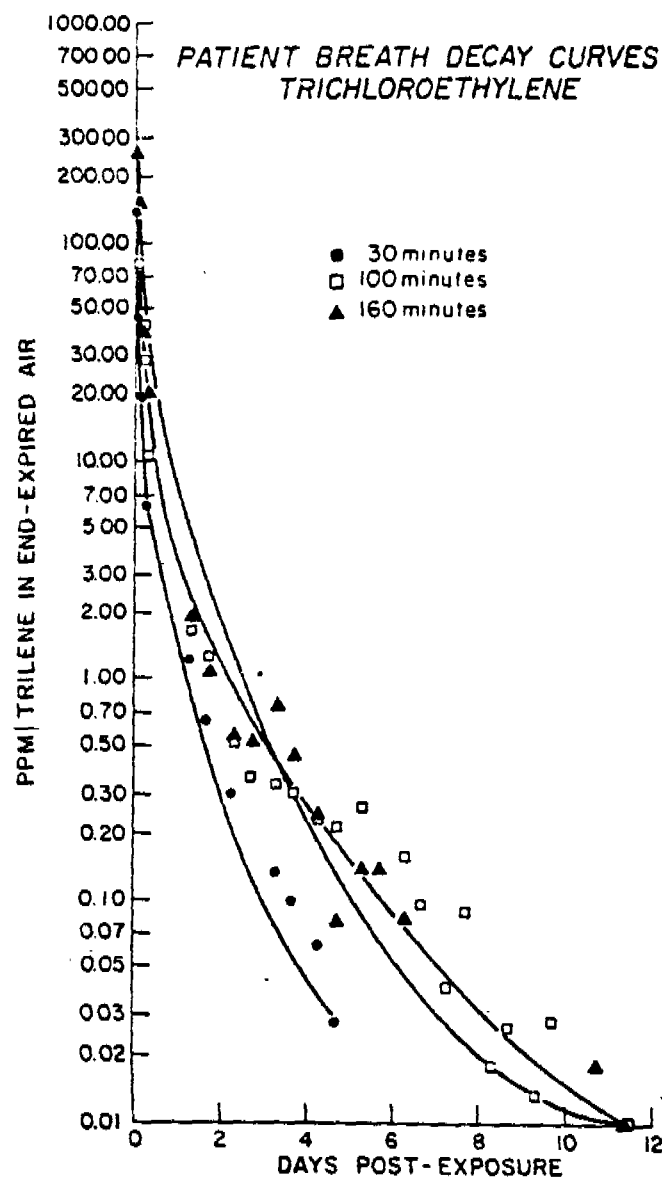


FIGURE 1. Trichloroethylene breath decay curves for three patients exposed to TCE anaesthesia: 30, 100, 160 minutes.

requires it? Our study of operating-room levels of TCE during anaesthesia has demonstrated that these levels are reached near the expiratory valve during cases when the anaesthetic machine and anaesthetist are partially enclosed in a tent of surgical drapes. Furthermore, 110 ppm was the lowest level studied by Salvini *et al.* and the concentrations impairing mental functions may be considerably lower.

The possible impairment of psychophysiological function by operating room concentrations of other anaesthetic gases should be studied.

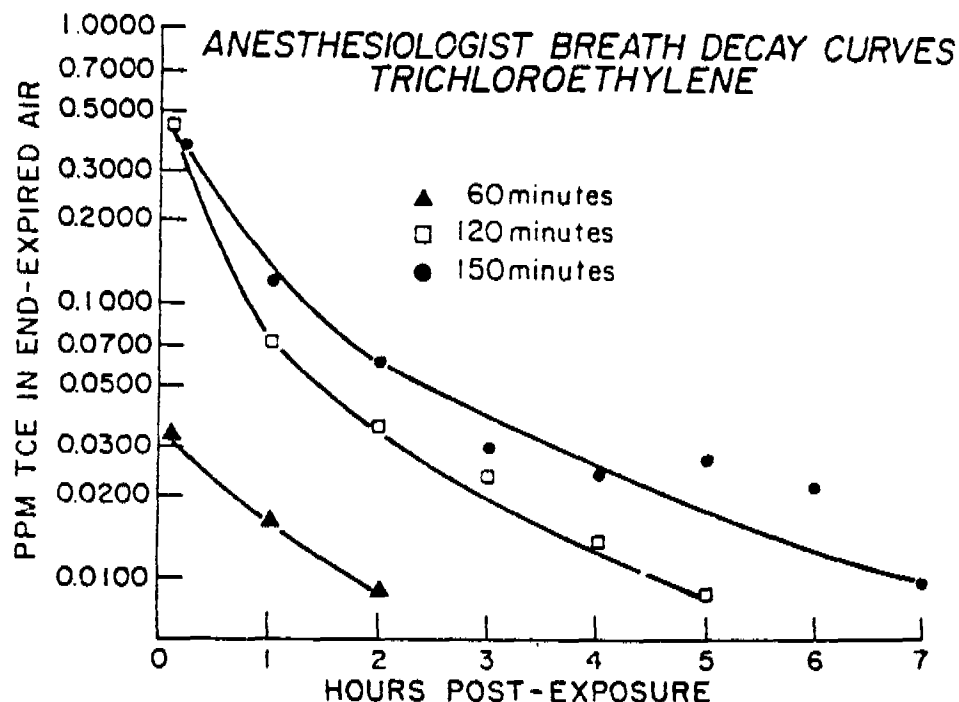


FIGURE 2. Trichloroethylene-breath decay curves for anaesthetists following occupational exposures of 60, 120, and 150 minutes.

RÉSUMÉ

Nous avons mesuré les concentrations de trichloréthylène aussi bien dans l'atmosphère de la salle d'opération et à la fin de l'expiration des anesthésistes au cours et à la suite de l'administration de trichloréthylène. La concentration la plus élevée de trichloréthylène dans la salle d'opération était de 103 ppm (parties par million) et est survenue durant une anesthésie où l'anesthésiste lui-même et la machine à anesthésie étaient partiellement enfermés dans une tente avec des champs chirurgicaux. La plupart des taux variaient entre 2 et 14 ppm. A la fin d'expiration des anesthésistes, le trichloréthylène était mesurable jusqu'à sept heures après un travail professionnel de routine.

Les concentrations de chloréthylène à la fin d'expiration des malades soumis à une anesthésie au chloréthylène étaient détectables jusqu'à onze jours après la fin de l'anesthésie.

ACKNOWLEDGMENTS

This project was supported by Veterans Administration Research Funds.

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 4 1944

CRANIAL-NERVE PALSIES WITH HERPES FOLLOWING GENERAL ANAESTHESIA

A REPORT FROM THE CENTRAL MIDDLESEX COUNTY HOSPITAL

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During a period of four months 13 cases of cranial-nerve palsies following general anaesthesia have occurred at this hospital. The cases occurred in three small groups, with free intervals of four and nine weeks between. Two of the affected persons died, while the remainder are at various stages of recovery. The degree of severity varied from subjective trigeminal anaesthesia only to a complete picture of encephalitis, but the main features were remarkably constant and readily recognized. Twenty-four to forty-eight hours after use of a general anaesthetic the patient complained of a sense of coldness, numbness, or tightness round the lips, which in most cases during the course of the next two or three days had spread to involve the whole distribution of the fifth nerve on both sides. This subjective anaesthesia was usually associated with analgesia and anaesthesia over the same area, and in nearly every case there was difficulty in swallowing solid food owing to its "getting lost in the mouth." Three of the cases also showed motor fifth-nerve weakness. About the third post-operative day, in the majority, there appeared circumoral herpes of the febrile type. At this time, in those persons showing further involvement, affection of other cranial nerves became apparent—e.g., diplopia, facial weakness, palatal weakness, and tremor or deviation of the tongue. In those cases which showed improvement this began on the fifth to the tenth day, and the milder cases recovered rapidly (almost completely in a fortnight), whereas the severer cases still had residual subjective changes after five months. The herpes had disappeared by the end of ten days. On no occasion did we observe affection of the first, second (including rough testing of the visual fields), ninth, or eleventh nerve, but all the other cranial nerves were involved in one or more cases. Taste over the posterior one-third of the tongue was not tested, and the ninth nerve may have been involved. Only one patient had an extensor plantar response, and that was unilateral. None ran unduly high temperatures during the post-operative period. Six vomited more severely than we normally expect after operation, and five were noticeably depressed, listless, or confused for two or three days. Three only complained of severe headache. A typical history is that of Case 4.

A Typical Case (No. 4)

A woman aged 25 was subjected to appendicectomy for acute appendicitis on July 30, 1943. Premedication was by morphine gr. 1/6 and hyoscine gr. 1/150. The anaesthetic employed was a combination of intravenous pentothal with cyclopropane and a little ether, given by closed circle with CO₂ absorption. The operation was a short one and the anaesthesia was without incident.

On Aug. 1 she complained that she had had a feeling of coldness of the face with double vision for 24 hours. At the same time there was some difficulty in opening and closing the mouth. On examination the left pupil was larger than the right. The reactions to light and accommodation were normal. There was double vision in all directions. The position of the false image indicated that the

diplopia was of third-nerve origin. There was no nystagmus and the fundi were normal. Hypo-algesia and hypo-aesthesia affected all the trigeminal field of each side. The corneal reflexes were diminished and the jaw-jerk was depressed. No muscular weakness affecting the fifth nerve could be detected. Subjectively the lips felt cold and the face numb and swollen. Food placed in the patient's mouth felt cold. There was bilateral facial weakness affecting the upper and lower face. No other abnormality could be detected in the cranial nerves. There was no neck rigidity or retraction.

The symptoms and signs remained unchanged until Aug. 2, when herpetic vesicles were found on the buccal mucous membrane on the left side of the mouth. These continued for three or four days. On Aug. 4 she complained of difficulty in swallowing. A lumbar puncture performed on the 6th yielded a clear fluid under normal pressure; no white cells were found. There was a gradual diminution in the cranial-nerve palsies; by Aug. 11 the difficulty in swallowing had disappeared, and by the 18th the diplopia had cleared. The scalp still felt abnormal. The skin over the forehead and the cheeks felt "swollen and stretched," and she complained of a peculiar tingling sensation around the nose. The tongue and the teeth still felt cold and numb. The pupils were equal in size and the external ocular movements were full. Hypo-algesia and hypo-aesthesia were present over the whole distribution of the fifth nerve, but around the nose stimulation with a pin produced an exaggerated reaction. There was still left facial weakness. She was transferred for convalescence on Aug. 27.

The patient was seen again on Oct. 7. She stated that she had had transient diplopia, when tired, up to a week before her visit. The upper lip still felt "twice its size" and the eyelids and the forehead seemed heavy. Since her discharge on Aug. 27 she had noticed involuntary twitchings of both sides of the face, of very short duration. There was a slight degree of diminution of sensation to pin-prick on the right side of the face, affecting all divisions, with a slight left facial weakness. No other abnormality was found in the central nervous system.

Table 1 summarizes the clinical aspect of the cases. In it are included only those which showed definite cranial nerve involvement; but it should be mentioned that in association with them we encountered three cases of unexplained herpes developing about the third post-operative day, without complications other than severe headache or transient tingling of the lips. The clinical features require no further comment, except that involvement was usually (but not always) bilateral, and that in some the subjective fifth-nerve changes were accompanied by very definite changes in sensation to pin-prick and light touch.

History of Two Fatal Cases

Necropsies were performed upon the two fatal cases. Since Case 8 differed from all the others, a brief history is given.

Case 8

This patient was a woman aged 56. On Aug. 4, 1943, a cholecystectomy was performed, the anaesthesia lasting about one hour. She received premedication with morphine gr. 1/6 and atropine gr. 1/100, and anaesthesia (pentothal, nitrous oxide, oxygen, and ether) was maintained through a naso-tracheal tube by a closed-circle technique. The operation and anaesthesia were smooth and without incident. Post-operatively she was somewhat slow in returning to consciousness, and vomited rather more than is usual. Next

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day she was apathetic, and in the evening she became delirious, with twitching round the mouth during the night.

On the following day she was ill and confused. Her left pupil was larger than the right, and was fixed and inactive to light. There was bilateral fifth-nerve analgesia with absent corneal and conjunctival reflexes. She had a gross tremor of the tongue, and marked incoordination of the arms, which was worse on the right than on the left. Her condition gradually deteriorated, and bilateral facial

enlarged prostate, bronchopneumonia, and some general oedema of the brain.

Histology.—Occasional small capillary haemorrhages were seen in sections through the pons and midbrain, together with small perivascular collections of lymphocytes in the substantia nigra. In addition to the lymphocytic cuffing, macrophages containing haemosiderin were found in sections through the cerebellum. The upper part of the medulla oblongata contained occasional collections of

TABLE 1.—Clinical Summary of Cases

No.	Sex	Age	Operation Date	Nature of Operation	Anaesthetic	Duration of Anaesthesia	Post-op Vomiting	Herpes	Cranial Nerves Involved	Comment
1	M	53	28/6/43	Bone graft	Pent., cyclo., O ₂ , induction—trilene maintenance	1½ hours	—	—	Subjective V	Not discovered until 4½ months later
2	F	21	28/6/43	Appendicectomy	Pent., cyclo., O ₂ , + a little ether	½ hour	+	+	V (all divs.) and motor XII	
3	F	19	28/6/43	"	" "	"	+	+	V (all divs.) and motor	Followed Case 2 on table
4	F	25	30/7/43	"	" "	"	—	+	III, V (all divs.), VII, X	
5	F	62	30/7/43	Cholecystectomy	Pent., cyclo. O ₂ , + a little gas-O ₂ -ether	1½ hours	±	+	III, V (all divs.), mainly subjective, X, XII	Followed Case 4 on table
6	M	41	2/8/43	Appendicectomy	Gas, O ₂ , ether, "to-and-fro" (on circle machine)	½ hour	+	+	Subjective right V (all divs.)	
7	F	45	3/8/43	Laparotomy	Pent., cyclo., O ₂	½ "	+	—	Subjective left lateral V (1 and 2 divs.), R, VII	
8	F	56	4/8/43	Cholecystectomy	Pent., gas, O ₂ , ether	1 "	—	—	III, V, VII, X, XII	Died in coma on 2nd post-operative day
9	F	46	17/8/43	Removal of cyst-adenoma of breast	Pent., trilene + O ₂ , induction—cyclo. maintenance	½ "	+	+	V (all divs.), R, VII	
10	F	39	21/10/43	Hysterectomy	Cyclo., O ₂ , + a little ether	1½ hours	±	+	III, V, VI, VII, VIII	Very severe headache, R. extensor plantar response
11	M	74	27/10/43	Cystoscopy and suprapubic cystotomy	Cyclo. + O ₂	½ hour	±	—	V (+ motor), L, VI, VII	Died on 16th post-operative day
12	F	18	27/10/43	Appendicectomy	"	35 mins.	—	+	V, R, VII	Under treatment for myasthenia gravis
13	F	35	27/10/43	Evacuation of uterus; severe blood loss	"	5 "	—	+	L, V, transient L, VII	Followed Case 12 on table

Pent.=pentothal. Cyclo.=cyclopropane. Gas=nitrous oxide. O₂=oxygen. Trilene=trichloroethylene.

weakness became apparent. During the afternoon she became stuporous, with jerking movements of the legs and arms. Lumbar puncture yielded 3 c.cm. of clear faintly yellow fluid under normal pressure; protein, 1.70 g. per 100 c.cm.; 14 polymorphs per c.mm. She died in coma at 10 p.m. on Aug. 6.

Necropsy was performed by Dr. W. Pagel 12 hours later: "The operation wound was sound. There was no gross abnormality of any organ except the brain, which showed marked oedema. Cultures of c.s.f. were sterile, and there was no meningitis."

Histology (Dr. Pagel).—There was no evidence of fat embolism anywhere in the parts examined. In all sections through the mid-brain and the floor of the fourth ventricle there was marked deposition of thready material in the perivascular lymph spaces (oedema). There were seen in addition a few vessels surrounded by a single row of lymphocytes, and a few capillary haemorrhages into the perivascular lymph spaces, together with collections of microglia in the neighbourhood of vessels. The ganglion cells in the central grey matter and the medulla oblongata were free from appreciable changes.

Summary of Case.—Marked oedema in the midbrain, pons, and medulla oblongata. Small capillary haemorrhages and beginning slight cuffing around the vessels. No changes in the ganglion cells. Portions of brain from the region of the affected nuclei were removed for animal inoculation.

Case 11

This patient, a man aged 74, was suffering from retention of urine due to an enlarged prostate (blood urea, 168 mg. per 100 c.cm.) and from chronic bronchitis with emphysema. He had auricular fibrillation, which was controlled by digitalis. A cystoscopic examination was made and suprapubic cystotomy performed under cyclopropane-and-oxygen anaesthesia, after premedication with morphine gr. 1/6 and atropine gr. 1/100. The anaesthesia lasted about three-quarters of an hour. Post-operative cranial-nerve involvement was extensive but not severe, and included the fifth nerve: subjective numbness in all divisions, with hypo-algesia and pins-and-needles sensation over the nose. His jaw deviated to the left. The palatal reflex was absent, although palate movement was normal. The sixth nerve showed slight left external rectus weakness, and the seventh nerve slight bilateral lower facial weakness. His chief difficulty lay in an inability to swallow solids, though he had no nasal regurgitation. Although suprapubic drainage was adequate he went progressively downhill. He was quite unable to swallow fluids towards the end, and died on the sixth post-operative day. At the necropsy, performed by Dr. L. C. G., the only findings of significance were an

microglia in star formations. Oedema was also present, but was much less intense than in Case 8. The small haemorrhages might be due to terminal respiratory embarrassment. In photomicrographs taken of sections from the two brains the most noticeable feature in each case was probably the oedema of brain and brain-stem, although there was no clear histological evidence of the cause of the condition.

Other Pathological Findings.—Lumbar puncture was performed upon nine of the patients during the first week. The pressure was never raised, and in all cases the cerebrospinal fluid was bacteriologically sterile. In only two cases was there a small increase of polymorphs (10 and 14 per c.mm.). In four the protein content was 0.04% or less, while the remainder contained 0.055%, 0.07%, 0.085%, 0.09%, and 1.7%.

Animal Inoculation.—We were fortunate in obtaining the help of Dr. C. H. Andrewes, of the National Institute for Medical Research, who performed many of the inoculations. Cerebrospinal fluid from five cases and portions of brain removed at necropsy from two cases (some glycerinated, some filtered through a 0.7 μ membrane and held at -70° C.) were injected intracerebrally or intrathecally into a total of 44 mice, 12 rabbits, and 1 rhesus monkey. No evidence of transfer of a virus infection was obtained.

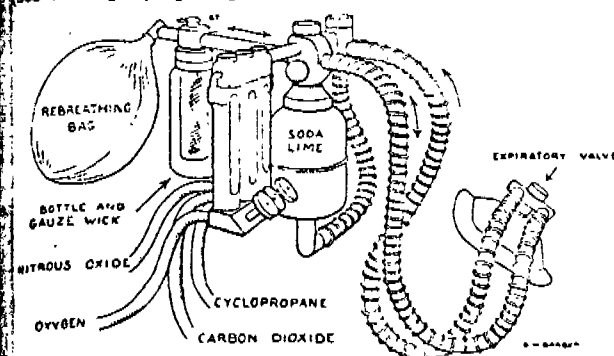
Theories of Aetiology

The cases described were operated upon by four different surgeons and anaesthetized by three different anaesthetists. None of them showed signs of anaemia or other complication upon the table. There was no evidence to incriminate any definite ward, but it was notable that all the anaesthetics were given in one theatre and all on the same type of machine. It seemed to us that the damage must have been directly due to the anaesthetic or to the lighting up of some latent virus infection, or both. The mode of anaesthesia and certain serological findings are presented with these possibilities in mind.

Anaesthetics

It will be observed from Table 1 that the anaesthetics were variable and that no one drug was common to all cases. The major surgery of the hospital is done in two operating theatres. The anaesthetic machine used in 12 of the 13 cases is one with which either a simple semi-open "to-and-fro" method may be used or else a closed-circle technique, with a soda-lime

canister incorporated to absorb the carbon dioxide. There is only one bottle on the machine. It contains a gauze wick. This wick retains a little of whatever anaesthetic drug has been in the bottle previously, and thereby contaminates the drug next used—e.g., ether following trichloroethylene, or vice versa (see accompanying diagram).



Although a number of tests had shown the bag and corrugated rubber tubing of the machine to be free of viable bacteria when swabbed immediately after use, this machine was sent to be sterilized in August. While it was away the same type of circle absorber was attached to a Boyle apparatus, and on this one case of palsy occurred (No. 9). In the other theatre a simple Boyle apparatus without soda-lime absorber is used, and on this there were no cases.

The anaesthetics administered were varied, but all except two were well-ried mixtures—namely, Cases 1 and 9, which received pentothal followed by cyclopropane and trichloroethylene, using the closed-circle technique. Ether, pentothal, and cyclopropane are drugs which have been used very extensively and have withstood the tests of time and experience. Trichloroethylene has been more recently introduced into anaesthetic practice, and has only been widely used in England since Hewer's report of 400 administrations and review of experimental work on animals (Hewer, 1942), although, in America, Striker and his colleagues were using it in 1935. Two reports of fifth-nerve palsy following the administration of trichloroethylene anaesthetics appeared during the past year (Hewer, 1943; McAuley, 1943). In the cases reported by Hewer impurities in the drug were considered to be the cause. Earlier reports in the German literature record cases of trigeminal palsy developing in industrial workers using trichloroethylene, toxic contaminants being regarded as a possible cause (Stüber, 1931; Jackson, 1934). Therefore, although this drug was used upon only two of our cases it was naturally suspect.

During the four months July to October 940 inhalation anaesthetics were administered in the two theatres, of which 600 were given in Theatre I (where all the cases occurred) and 340 in Theatre II. Each main drug, associated with others, was used in the following proportion of cases: ether 35%, cyclopropane 24%, trichloroethylene 16%, and pentothal 25%. Nitrous oxide was used in many and oxygen in all. On the circle machine in Theatre I there were 80 administrations of trichloroethylene, and on the Boyle apparatus in Theatre II there were 65.

These figures appear to give very little clue to the problem, but the occurrence of all the cases on the circle machine led us to suspect that a possible toxic agent might result from the interaction of traces of trichloroethylene with soda-lime or the other drugs used. It has been pointed out (Morton, 1943; Stüber, 1931) that chemical reactions may occur between trichloroethylene and alkalis, particularly when heated. Owing to its low volatility trichloroethylene is not regularly used on a closed circuit, but during the period under review this was done on several occasions (including Cases 1 and 9). It is also conceivable that in our anaesthetic machine (described above) trichloroethylene used by the "to-and-fro" technique might linger in the machine or in the gauze wick, and thus be carried over into the soda-lime when a subsequent anaesthetic was given by closed circuit. In either case there would be definite possibilities of chemical reactions occurring, especially since we have noted temperatures of the order of

70° C. in the soda-lime canister. Our suspicion was strengthened by the presence of an unusual sweetish penetrating odour frequently noted about the machine during this period. (The odour was subsequently reproduced by incubating trichloroethylene with soda-lime.)

Dr. H. E. Cox, D.Sc., F.I.C., undertook to analyse the drugs used, paying particular attention to possible chemical reactions or impurities. A summary of his report is as follows:

(1) The cyclopropane, ether, and trichloroethylene fulfilled the prescribed conditions of purity. (2) There is no evidence of any change, under the conditions of administration, in (a) cyclopropane or (b) ether which would cause injury. (3) There is evidence of reaction between trichloroethylene and soda-lime, and (4) this reaction produces dichloroacetylene. This substance readily combines with oxygen to form phosgene, carbon monoxide, and carbon dioxide, but does not further oxidize in the presence of sufficient excess of trichloroethylene. (5) The reaction is greatly stimulated by rise of temperature in the soda-lime; it proceeds markedly even at blood heat. (6) There is no evidence of direct formation of oxidation products in the trichloroethylene without soda-lime. (7) The effects of dichloroacetylene in trichloroethylene are not known, but should be ascertained. (Dichloroacetylene is a substance explosive in the presence of limited oxygen.)

Experiments are at present being undertaken to find out the physiological effects of the reaction products of trichloroethylene and soda-lime. Dr. Cox's observations have been confirmed by the Department for Research in Industrial Medicine of the Medical Research Council, which is meanwhile making investigations of the toxicity of these substances to rats. We ourselves have obtained some striking preliminary results with rabbits. The animals were subjected to anaesthetic mixtures consisting of trichloroethylene plus 0.5–1.0% dichloroacetylene or of ether plus trichloroethylene plus 0.5–1.0% dichloroacetylene given in the same way, and on the same anaesthetic machine as was used for the cases under review. Each animal received the mixture under test for three periods of about 20 minutes at five-day intervals. Anaesthesia was light, and difficult to maintain when ether was not used, and the rabbits appeared to recover quickly and to show no untoward symptoms. After the third anaesthesia one rabbit was killed by an overdose of anaesthetic, and the other was killed seven days later by stunning. Histology of both was very similar, and showed little change in any organ except the brain and the liver, in which there was slight necrosis. In the brain there was extremely marked perivascular cuffing and glial proliferation throughout, with numerous foci of necrosis. There was even a marked meningeal reaction, and the picture at first sight was one of encephalitis. We have never met such a histological picture in any other of our rabbit stock, and, although further work is necessary, have no hesitation in attributing it to the anaesthetic. On the strength of this preliminary evidence it would appear advisable not to use trichloroethylene in the presence of soda-lime.

Temperature

It is well known that when artificial hyperthermia is induced in normal persons a high proportion (about 70%) develop labial herpes 2 to 3 days later (Keddie, Rees, and Epstein, 1941). A combination of anaesthesia with overheating of the patient by heat generated in the soda-lime might have provided a possible explanation for the herpes, the palsies, and the peculiar incidence. In a number of cases the temperature in the rubber tubing leading to the patient was recorded, the maximum reached being only a few degrees above room temperature. The axillary temperatures of the patients rarely varied more than $\pm 1^\circ$ F. during operation. Although none of these patients developed symptoms there was no evidence to support this idea as a possible explanation.

Virus Infection

The occurrence of herpes on the third day in nine out of the twelve patients who survived this period was particularly striking in view of the fact that none of them had colds or any other condition commonly associated with herpes, and that half of them after careful questioning denied ever having previously had this condition. Among other operation cases the incidence at that time, in the absence of colds, was very low.

The lesions were characteristic of herpes febrilis, consisting of numerous discrete vesicles upon the mucocutaneous junction of the lips, the chin, and occasionally the buccal mucous

membrane and soft palate. In four cases successful transfer to rabbits was obtained by intracorneal inoculation of vesicle fluid, and the strains behaved typically. One strain (Case 10) was studied particularly by Dr. C. H. Andrewes and ourselves, and was adapted to rabbit testicle and skin, to guinea-pig pads, and to mouse brain. None of the strains was particularly neurotropic in rabbits or guinea-pigs, although direct intracerebral inoculation in a rabbit produced death from encephalitis after some weeks.

Herpetic encephalitis in man has never been authenticated, although during the epidemic of encephalitis lethargica in Europe after the last war numerous attempts were made to incriminate the virus, and its isolation was claimed from the brains of the affected and of normal persons (Doerr and Berger, 1922; Flexner and Amoss, 1925). Studies by Andrewes and Carmichael (1930) and by Brain (1932) showed that 70 to 75% of hospital patients have antibodies to herpes in their blood. In the majority of such persons overt lesions can be produced by artificial hyperthermia, intravenous T.A.B. vaccine, lobar pneumonia, meningococcal meningitis, the common cold, etc. Herpes occurs occasionally after injection of the Gasserian ganglion (Harris, 1937).

All the cases showed a definite incubation period between operation and the first appearance of symptoms, ranging from 24 hours to three days. This is very short, by accepted standards, for a virus infection. The post-mortem findings, on the other hand, were not inconsistent with an encephalitis, and were comparable with descriptions of some of the findings in the encephalitis lethargica epidemic. In the absence of a completely satisfactory "toxic" explanation, it was considered worth while to investigate the sera of these patients for antibodies against the herpes strain from Case 10 and another strain isolated at the National Institute for Medical Research by Dr. Andrewes. The viruses were adapted to the rabbit's skin, and each serum was tested for its power to inhibit the production of lesions by 5 to 10 infective doses of virus injected intracutaneously. The results are given in Table II.

TABLE II.—Results of Tests for Antibodies against Herpes

Case No.	Herpes	Herpetic History	Time of taking Serum after Operation	Neutralizing Antibodies	
				Strain 10	M.R.C. Strain
1	+	-	13 weeks	+	-
2	+	-	19 "	+	-
3	+	-	6 "	+	-
4	+	-	4 days	+	-
5	+	-	3 "	+	-
6	+	+	Not done	-	-
7	+	-	7 days	+	-
8	+	-	2 "	+	-
9	+	-	11 "	+	-
10	+	-	6 weeks	+	-
11	+	-	4 days	+	-
12	+	+	1 day	+	-
13	+	+	1 "	+	-

It is evident that every serum contains antibodies against both strains. The most significant samples are the early ones from patients without herpetic histories, since in these cases the formation of antibodies would have been too rapid to be due to the herpes occurring at that time, quite apart from the fact that some never developed the condition. Herpes antibodies are commonly found in persons with latent infection, and the implication is that all these patients had latent herpes.

We were not able to demonstrate any immunological difference between the two strains by cross-protection tests, and cannot claim unusual virulence for the strain 10 studied. If herpes or any other virus infection is involved it must have been "lit up" by the anaesthetic. There is some experimental evidence for this possibility in the observation of Fiala (1943) that subdural or intravenous injection of vaccinia virus in rabbits is not normally followed by encephalitis, but is so if the rabbits are under urethane anaesthesia; or the work of Silberstein and Hoff (1925), who showed that a normally latent encephalitis virus could be activated in dogs with an Eck fistula by feeding with a diet of meat only. Argument by analogy is dangerous, however, and in the absence of positive findings from the inoculation of post-mortem material into susceptible animals we are unwilling to do more than suggest the possibility that herpes virus played a part.

Discussion

The clinical evidence favours two possible theories, or a combination of both, but the experimental results are strongly in favour of a toxic theory. If the latter is adopted there must have been great susceptibility, since one anaesthesia (Case 13) was of five minutes' duration and the patient developed well-marked palsy.

The only drug which could be incriminated is trichloroethylene plus soda-lime, and this only on the assumption that it could have persisted in the machine or in the soda-lime between the anaesthesias in which it was used. On two occasions as long as three days elapsed between the use of trichloroethylene and the anaesthetic which was followed by palsies, and during the intervals there had been given nine and twelve closed-circuit cyclopropane or ether anaesthesias respectively on the same machine without any ill effects. On another occasion trichloroethylene was followed on three succeeding days by varied anaesthetics which developed palsies. Four closed circuits, but no further trichloroethylene, had meanwhile been administered. Seven only of the cases were associated with the use of trichloroethylene on the same day, and of these two actually received the drug in closed circuit. It should be mentioned that the soda-lime was periodically "resterilized" for any time up to two or three days, and the use of contaminated soda-lime at a later date might explain the intervals between trichloroethylene administration and the anaesthesias which were followed by palsies. We consider it to have been a definite possibility that the majority of the patients who were anaesthetized on the circle machine were subjected to this risk. The fact that only a small proportion showed symptoms would mean that there must be great variation in susceptibility. Such variations are well known in toxicology.

The first case of the series was missed until 4½ months later, when a chance remark of the patient's drew attention to his lesion. It seems to us possible that mild cases may have occurred elsewhere, and the facts recorded above have been published in the hope that the observations of others may help to shed light upon the problem.

It is now over three months since we ceased using trichloroethylene in association with soda-lime, and although many trichloroethylene anaesthesias, some lasting up to three hours, have been given, no further palsies have occurred.

Summary

Thirteen cases of cranial-nerve palsy following general anaesthesia are reported. The nerves involved were mainly the fifth and seventh, but the third, fourth, sixth, tenth, and twelfth were involved in some cases. The condition was associated with labial herpes in 9 cases.

No anaesthetic drug was common to all cases, but all were administered on a circle absorber anaesthetic machine.

Evidence is given for chemical reactions between soda-lime and trichloroethylene in the system, with the production of dichloroacetylene.

Preliminary results show that this substance is toxic to rabbits.

Antibodies against herpes were found in the sera of all cases.

The aetiology of the condition is discussed. It is concluded that until further investigations have been made trichloroethylene should not be used where there is any possibility of its coming into contact with soda-lime.

Our thanks are due to Dr. C. H. Andrewes, Dr. Donald Hunter, Dr. C. L. Hewer, Dr. J. G. Greenfield, and Dr. H. E. Cox for much help and advice.

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