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HEXAFLUORODIETHYL ETHER AS USEFUL CONVULSANT IN THE TREATMENT OF MENTAL ILLNESS

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ABSTRACT OF THE DISCLOSURE

Hexafluorodiethyl ether $CF_3CH_2OCH_2CF_3$ is prepared by the reaction of 2,2,2-trifluoroethyl p-toluene sulfonate with an alkali metal 2,2,2-trifluoroethanolate. The ether is a useful convulsant effective for the treatment of mental illness.

This application is a continuation-in-part of application Ser. No. 657,482, filed May 7, 1957, now abandoned.

This invention relates to a novel and highly beneficial method, and composition for use therein, of convulsive therapy.

More particularly, the invention concerns the compound 2,2,2,2',2',2'-hexafluorodiethyl ether (hereinafter referred to more simply as hexafluorodiethyl ether), having the formula $CF_3CH_2—O—CH_2CF_3$, its method of preparation, and uses thereof. In accordance with this invention, it has been found that hexafluorodiethyl ether is physiologically active as a strong convulsant, and that it may be administered to patients, as hereinafter more fully described, for inducing a convulsive state having a desirable therapeutic effect, particularly in the treatment of certain types of mental illness.

Convulsive shock therapy as a treatment for mental illness is a development of relatively recent origin. Its earliest forms are generally conceded to have been by means of pharmacologic provocation in which certain pharmacologic agents were employed to produce a desired state of convulsion in the patient undergoing treatment. Among the agents that have been utilized for this purpose is Metrazol (a trademark for one brand of pentamethylenetetrazole) and insulin. In addition, other pharmacologic agents including picrotoxin, coriamyrtin, ammonium chloride and cyclohexylethyl triazol have been suggested and investigated for this purpose. However, various difficulties, including several fatalities with the latter group of agents, were encountered and Metrazol is presently considered to be the standard preparation for pharmacologic convulsive therapy.

More frequently used at the present time, however, and generally preferred over the pharmacologic method of provocation, is the so-called electroshock, or electric convulsive therapy. This treatment, as the name suggests, involves the provocation of convulsions by the passage of an electric current through the patient's body. Conventionally, this is accomplished by suitable apparatus having electrodes which are applied to the patient's head and associated electrical means for delivering controlled amounts of electric current of a controllable potential for a selected interval.

The common characteristic of these methods of therapy, previously employed, is that of producing in the patient a state of shock, normally accompanied by a convulsive seizure. Although modified patterns of the convulsive seizure, and some sub-convulsive treatments, have been investigated, the treatments considered most efficacious in the treatment of mental illness involve evoking convulsions of the grand mal type, extending through the tonic and clonic phases with the loss of consciousness usually at the tonic phase and temporary cessation of respiration, usually accompanying supervention of the clonic phase. Various reasons may be attributed to the specific action of the electric stimulus and the pharmacologic agents in eliciting such shock, or convulsive phenomena, which are not involved in the disclosure of the present invention. Generally, the primary object of these types of mental treatment is to utilize the effect which the shock and accompanying convulsive seizures, produced by such means, may have on the mental disease process. Such convulsive treatments are frequently administered accompanied by psychotherapy, particularly in neurotic patients.

A considerable measure of success has been afforded by these methods of convulsive therapy in the treatment of mental illness, particularly when it is understood that prior to the advent of such techniques a prognosis of incurability would have been made for the majority of these patients. However, notwithstanding such important advances, there are several extremely objectionable complications attendant upon these presently available methods of therapy. For example, with the use of pentamethylenetetrazole an intense feeling of apprehension is produced in the patient just prior to the onset of its convulsive effect. Patients so dread this feeling of apprehension and sense of overwhelming disintegration that a tremendous resistance has been encountered to this form of treatment. There is also the problem in this method, as well as with other pharmacologic agents, that are administered intravenously or intramuscularly, in proper dosage. Thus, only an approximation of the required dosage can be made for any particular patient, since the convulsive shock does not set in until after a substantial period of time following injection of a sufficient dosage. Frequently, subsequent injections are required when the initial dosage has been insufficient. This contributes to and exaggerates the characteristic sense of apprehension experienced by the patient with pentamethylenetetrazole. Furthermore, even when successful or satisfactory administration may be performed, the contra-disposition of the patient to this therapy tends to negate is effectiveness in the overall scope of the psychiatric treatment. Largely for these reasons electroshock therapy has replaced, generally, the pentamethylenetetrazole method. However, the electroshock method still has associated with it marked feelings of apprehension on the part of the patient, owing, in part, to the ominous appearance of the apparatus and nature of the physical procedure involved. Of more immediate material difficulty, however, in electroshock treatment, is the extreme strain that is produced on the patient's skeletal members by the instantaneous muscular distortions evoked by the convulsive syndrome. Oftentimes, because of the abruptness and severity of the convulsions fractures result. In addition, the nature of such treatment, especially its physical severity, makes its use contra-indicated in many cases, for example, such as where the patient is suffering from diseases such as heart ailment. Still further, there is the problem of apnea which, characteristically, is produced for undesirably prolonged periods of electroshock therapy. A substantial portion of the fatalities encountered in this form of treatment have resulted from respiratory failure. In addition, as a further limitation of this method for mental therapy, there is the temporary memory deficit experienced in almost all of the patients subjected to this treatment. While not of permanent nature, this mental aberration frequently interferes with any psychotherapeutic clinical procedure carried out in conjunction with the electroshock treatments.

Accordingly, it is one of the objects of the present invention to provide a new method for producing a convulsive state, having a therapeutic effect upon mental disorders, which avoids many of the serious objections presented by methods of convulsive therapy heretofore employed.

A further object of the invention is to provide a new convulsive agent characterized by its ability to provoke a convulsive syndrome comparable to that produced by administration of pentamethylenetetrazole or the use of electroshock, and which is substantially free from objectionable toxic reactions or other undesirable side effects.

A further object of the invention is to provide a new convulsive agent, useful for therapeutic purposes, which is rapid acting and the proper administration of which may be determined by direct observation of the patient's response thereto.

A further object of the invention is to provide a volatile convulsant agent adapted to be administered by inhalation.

A further object is to provide a method for the preparation of hexafluorodiethyl ether, employed in accordance with this invention as a convulsive agent.

Other objects and advantages of the invention will be better understood by reference to the following description in which the compound hexafluorodiethyl ether, its method of preparation, and the method of its employment as a convulsive agent are more fully related.

Hexafluorodiethyl ether, as prepared for use in accordance with the present invention, has been found to be a clear, colorless mobile liquid, B.P. 63.9° C./760 mm., n_D^{20} 1.2797. Additional properties have been determined to be as follows: freezing point, below —80° C.; specific gravity

$$1.4171\ \frac{20°C.}{20°C.}$$

viscosity, 0.620 centipoises 20° C.; surface tension, 18.6 dynes per cm.; solubility in water, 0.2% by wt.; solubility of water in, 0.1% by wt. The compound is extremely stable: water, acids and alkali have no effect on the ether linkage; the fluorine atoms can be removed only under vigorous conditions such as fusion with sodium. The vapors of the agent have been found to be nonflammable at room temperatures and under the ordinary circumstances that are encountered in its employment as described herein.

The following examples describe certain pharmacologic tests conducted with hexafluorodiethyl ether as a convulsive agent.

(1) PRELIMINARY STUDIES

Four white male rats were placed in individual anesthesia jars (approx. 3.4 liters) with a pledget of cotton on which was placed 0.5 cc. of hexafluorodiethyl ether. The rats convulsed within 30 seconds. They showed clonic and tonic convulsions and opisthotonus.

Four white male mice were placed in the same anesthesia jar as before with the cotton removed. The remaining vapors caused immediate convulsions to occur in the same manner as with white rats.

One white male rabbit received 1.5 cc. of hexafluorodiethyl ether on a pledget of cotton placed in a bell jar, which resulted in convulsions in about 5 minutes. It showed opisthotonus almost identical with strychnine convulsions. The legs became extended and rigid. The animal recovered in a few minutes.

One white male cat received 1.5 cc. of hexafluorodiethyl ether in the same manner as the rabbit and experienced the same type of convulsions. It also recovered within a few minutes.

Each species exhibited the same convulsive seizures. Clonic jerks of the body occurred at the onset, followed by tonic contraction. Salivation and defecation were observed in the recovery.

All animals exposed to the vapors of hexafluorodiethyl ether survived an observation period of four days.

(2) CONVULSIVE THRESHOLD

(A) White male rats weighing 250–300 g. were placed in anesthesia jars (3.4 liters) with soda lime. A stream of

TABLE 1

	Amount hexafluorodiethyl-ether ml.	V./V. percent [2]	Onset of Convulsions Secs.	Remarks
Rat No.:				
1	0.04	0.20	--------	No convulsions in 5 min.
2	0.04	0.20	--------	Do.
3	0.04	0.20	--------	Do.
4	0.04	0.20	35	Convulsions confined to front legs only.
5	0.05	0.25	------	No convulsions in 5 min.
6	0.05	0.25	240	Few mild head jerks confined mainly to fore limbs.
7	0.05	0.25	--------	No convuleions in 5 min.
8	0.05	0.25	--------	Do.
9	0.05	0.25	75	Full convulsions.
10	0.05	0.25	80	Do.
11	0.05	0.25	45	Do.
12	0.05	0.25	80	Do.
13	0.06	0.30	45	Do.
14	0.06	0.30	155	Do.
15	0.06	0.30	--------	No convulsions in 5 min.
16	0.06	0.30	65	Full convuslions.
17	0.06	0.30	95	Do.
18	0.06	0.30	40	Do.
19	0.06	0.30	--------	No convulsions in 5 min.
20	0.06	0.30	50	Do.
21	0.07	0.35	40	All of this group convulsed continuoulsy. They were removed from jar and survived.
22	0.07	0.35	50	No convulsions in 5 min.
23	0.07	0.35	60	All of this group convulsed continuously. They were removed from jar and survived.
24	0.07	0.35	80	Do.
25	0.1	0.5	35	Full convulsions.
26	0.1	0.5	95	Do.
27	0.1	0.5	70	Do.
28	0.1	0.5	75	Do.
29	0.1	0.5	[1] 40	Do.
30	0.1	0.5	[1] 50	Do.
31	0.1	0.5	90	Do.
32	0.1	0.5	95	Do.

[1] Rats 29 and 30 placed in jar that had not been completely flushed out.

[2] V.V. percent is the volume percent concentration of the vapor of hexafluorodiethyl ether, expressed as 100 times the ratio of the equivalent gaseous volume of the agent to the total volume of the jar enclosure,

air was passed through the jar at a rate of 2 to 3 bubbles per second in the washing bottle. Hexafluorodiethyl ether was sprayed onto a gauze square placed on the wire floor of the bottle. The following data, given in Table I, are the results of such tests on 32 rats, showing the dosages administered and the times of response.

The threshold concentration for the convulsive syndrome in the rat based upon the above data is about 0.20% v./v. or 12 parts liquid hexafluorodiethyl ether per million parts air. For rapid convulsions in all animals a concentration of 0.35 v./v. percent is required. Is it clear that much individual variation in reaction time prevails among the animals at a constant dose level.

(B) A standard oxygen cylinder was filled with a mixture of 1% hexafluorodiethyl ether vapor, 30% oxygen, and 69% nitrogen. A 750 cc. percolator was arranged with entrance and exit lines to act as a vessel. The above 1% mixture was diluted by way of a Y joint with a known volume of air to give the appropriate mixture. The vessel was flushed with several liters of the appropriate mixture and the rat inserted with a positive pressure of gas passing through the vessel. The stopper was instantly inserted and the period required for the convulsive seizure noted. The following Table II summarizes the results obtained with 18 rats.

TABLE II

	Conc. of hexafluorodiethyl ether		Time for onset of convulsions, seconds	
	P.p.m., W./v.[1]	v./v., percent		
Rat No.:				
1	81	1.0	20	Average 23.
2	81	1.0	26	
3	40	0.5	20	Average 17.
4	40	0.5	11	
5	40	0.5	20	
6	27	0.34	140	Average 79.
7	27	0.34	43	
8	27	0.34	125	
9	27	0.34	38	
10	27	0.34	95	
11	27	0.34	59	
12	27	0.34	45	
13	20	0.25	225	Average 183.
14	20	0.25	240	
15	20	0.25	85	
16	20	0.25	(2)	
17	20	0.25	(2)	
18	20	0.25	(2)	

[1] P.p.m. w./v. is the concentration of hexafluorodiethyl ether in parts per million where W is the weight of hexafluorodiethyl ether in gms. and V is the total volume of the gases in milliliters.
[2] No convulsions.

From these data it appears that in the rat the threshold concentration for rapid convulsions lies somewhere between 0.25 and 0.37 v./v. percent. Further, no speed in onset appears to be gained from 1% over 0.5%.

(C) Data on the threshold concentration with monkeys and dogs were obtained as listed in Table III, using a closed-circuit type of anesthesia equipment with a carbon dioxide absorber and a suitable face mask. Hexafluorodiethyl ether was introduced to the closed circuit using the method of the preceding experiment. The data in Table III show the concentrations of hexafluorodiethyl ether and the times of response.

TABLE III

		Conc. of hexafluorodiethyl ether			
Animal	No.	P.p.m., w./v.	v./v. percent	Onset time, seconds	Remarks
Monkey	1	40	0.50	30	
	2	81	1.0	40	Violent and lasted for several minutes after withdrawal of agent.
	3	40	0.50	40	Full recovery.
		81	1.0	30	More severe and of longer duration.
	4	81	1.0	40	Severe and several minutes duration.
Dog	1 (8 kg.)	81	1.0	45	Not severe.
	2 (6 kg.)	81	1.0	95	Do.

It appears on the basis of the above that in larger animals 1.0% produces a convulsion more rapidly and of a more positive and severe nature.

(3) ANTIDOTAL STUDIES IN RATS

Experiments were conducted on rats to attempt to antidote the convulsive syndrome of hexafluorodiethyl ether. In 6 animals 30 mg./kg. of Pentobarbital Sodium was injected intraperitoneally. After complete sedation 0.1 ml. of hexafluorodiethyl ether was given in the usual anesthesia jar (0.5% v./v.). Some twitching and tremore occurred but no convulsions and the rats then slept. Animals appeared normal after awakening. Thiopental sodium likewise afforded protection in 4 animals. The administration of Fluoromar (trademark for the anesthetic agent 2,2,2-trifluoroethylvinyl ether) and Tridone (trademark for trimethadione, an anti-convulsant) prevented the convulsive syndrome in 4 animals each. The injection intraperitoneally of 400 mg./kg. of Mephenesin 5 minutes before exposure afforded little protection in 4 rats. Dilantin sodium, 30 mgm./kg., given intraperitoneally one-half hour before exposure also was of little effect in 8 rats.

(4) STUDIES IN CONNECTION WITH RESERPINE AND CHLORPROMAZINE

In addition to the antidotal studies above described, the effects of two tranquilizing drugs, namely chlorpromazine and reserpine, on hexafluorodiethyl ether-induced convulsions were evaluated. The threshold convulsive does and the time of onset of convulsion were measured before and after treatment with the tranquilizing drug.

Reserpine was administered intramuscularly to the groups of rats (8 rats per group). The rats in Group I received 25 mgm. per kgm. body weight 24 hours before exposure to hexafluorodiethyl ether. The results showed that following treatment with reserpine at the dose mentioned there was increased sensitivity of the rats to the convulsive drug. Before reserpine was given the mean threshold convulsive dose was 0.053 cc. After reserpine-treatment the mean threshold convulsive dose was 0.035 cc. The time of onset of the convulsive seizure was more rapid following reserpine, specifically, from a mean of 5 mins. 1 sec. to a mean of 3 mins. 17 secs. Rats in Group II were given 1 mgm. reserpine per kgm. body weight per day for three days. One-half hour after the third injection of reserpine the rats were exposed to the convulsive agent. There was no marked change in either threshold convulsive dose (the mean dose before reserpine was 0.053 cc., while after reserpine it was 0.049 cc.) or time of onset of convulsion (before reserpine the mean value was 49 secs., and after reserpine it was 36 secs.).

Chlorpromazine was injected intraperitoneally into two additional groups of rats (8 per group). As with the reserpine studies above, threshold convulsive dose and time of onset of convulsion were recorded before and after treatment with chlorpromazine. Group I received a single dose of chlorpromazine, 5 mgm. per kgm. body weight, and one-half hour later was exposed to hexafluorodiethyl ether. There was no appreciable change in mean threshold convulsive dose or time of onset of the convulsion before and after administration of the tranquilizing drug. The rats in Group II received chlorpromazine over a four-day period (5 mgm. per kgm. per day), and one-half hour after the fourth dose, were exposed to the convulsive agent. There was a slight decrease in the threshold convulsive dose (before chlorpromazine the mean value was 0.051 cc., and after chlorpromazine it was 0.041 cc.) and in the time of onset of convulsion (from a mean of 4 mins. 54 secs. to a mean of 3 mins. 54 secs.).

Single doses of chlorpromazine, 5 mgm. per kgm. body weight, were also given intraperitoneally to one dog (7.1 kgm.) and two monkeys (4.0 and 2.6 kgm. respectively).

There was no appreciable difference in the threshold convulsive dose of hexafluorodiethyl ether or in the time of onset of the convulsion before and one-half hour after the administration of chlorpromazine.

(5) ELECTROENCEPHALOGRAPHIC STUDIES

Eight dogs and 3 monkeys were lightly anesthetized by intraveous injections of thiopental sodium. Hexafluorodiethyl ether (0.5 cc.) was introduced in a vapor through an anesthesia mask. Prior to, during and after the inhalation, electroencephalograms were recorded.

The typical seizure pattern occurred within ½ to 1 minute after inhalation was begun and continued for 5 to 10 minutes. None of the animals showed any gross ill effects from the exposure. In one of the dogs and one of the monkeys exposed to hexafluorodiethyl ether, 10 mgm./kgm. of Metrazol was injected intravenously for comparison of the cerebral effects. There was a striking resemblance between the hexafluorodiethyl ether and Metrazol-induced cortical dysrhythmias.

Under Pentothal anesthesia the onset of a convulsive type brain wave pattern is slightly delayed but the diffuse slow wave pattern ("sleep pattern") is replaced with high voltage 3–4/second multiple spike and slow waves, typical of the myoclonic type of petit mal convulsive pattern, becoming dominant. With anesthetized animals, the high voltage multiple spiking of the tonic phase is not observed at the dosage used in these tests.

The administration of hexafluorodiethyl ether in the nonsedated animal elicits as the most typical response the production of high voltage 3–4/second slow wave and spike which rapidly become a multiple spike and 3–4/second slow wave discharge. This is soon followed by high voltage multiple spiking in the "tonic" phase of the convulsion.

The EEG response to hexafluorodiethyl ether indicates a major convulsive (myoclonic) type of cerebral dysrhythmia. The multiple spiking seems to be slightly decreased by premedication with barbiturates, at least as far as the continued grand mal type of multiple spiking is concerned. The cerebral discharge closely resembles that seen in the myoclonic type petit mal discharge and suggests a locus of action in the centrencephalic system of the brain.

(6) LOCUS OF ACTION

The injection of 0:05–0.10 cc. of hexafluorodiethyl ether into the dorsal lymph sac of frogs weighing 20 to 25 gm. evoked typical convulsive seizures within 5 minutes. Decerebration did not obliterate the seizure. Further destruction of the medulla prevented the convulsivion when the spinal cord was intact. In a frog with the cerebrum and medulla destroyed and the cord intact, the injection of hexafluorodiethyl ether into the dorsal lymph sac produced no convulsions. Locally there were no movements in the leg or muscular twitchings. These experiments were repeated on 9 additional animals. The convulsions resembled those of picrotoxin and appear to originate in the mid-brain and/or medulla in the frog.

(7) EFFECT ON DOG UPON INTRAVENOUS INJECTION

One cubic centimeter of hexafluorodiethyl ether was dispersed in 10 cc. of Polysorbate-80 and diluted to 25 cc. with normal saline. A 15 kgm. unanesthetized dog received 7 mg./kgm. of this dispersion intravenously. The conculsive syndrome ensued within a minute and prevailed for 10 minutes, after which the animal remained lethargic for about one hour. It is likely that the hypotensive response in the dog to Polysorbate-80 was responsible for the inactivity of the animal. The animal recovered and after 24 hours showed no gross ill effects from the injection.

(8) EFFECT ON THE ECG

A dog weighing 14.3 kgm. was given 30 mg./kgm. of Pentobarbital Sodium to produce anesthesia, and was arranged for EEG and ECG recording. The anesthetic mask was applied, and 0.5 cc. of hexafluorodiethyl ether was administered as previously described. When the cerebral effect prevailed as shown by the EEG, the ECG was recorded. The pattern and amplitude of the control and hexafluorodiethyl ether electrocardiograms were not significantly different in leads I, II and III. Hexafluorodiethyl ether evoked a slight tachycardia. During the period of hexafluorodiethyl ether cortical activitiy there was a transient fall in blood pressure of 10 to 15 mm.

(9) EFFECTS OF REPEATED EXPOSURE

Eight rats were exposed on alternate days to hexafluorodiethyl ether vapor 56 p.p.m. for four exposures. Eight additional animals received 30 mgm./kgm. of Metrazol at the same time periods, and 8 rats were exposed to diethyl ether (0.25 cc. per 3.4 liters). After four exposures 3 animals of each group were killed by decapitation and their brains, liver, kidneys and bone marrows examined histologically. There were no lesions in the hexafluorodiethyl ether-treated group that could in any way be associated with the action of the compound. In one of the pentamethylentetrazole treated animals there appeared evidence of chronic meningo-encephalitis.

Eight rats were exposed to convulsive doses of hexafluorodiethyl ether on five consecutive days. During the convulsive seizure on the fifth day blood was collected by cardiac puncture or exsanguination. Blood samples were likewise taken from a control group of 4 rats. Blood studies revealed no significant changes in blood urea nitrogen, glucose and calcium levels. The hematocrit was not appreciably elevated. Of the data on white and red cell counts and hemoglobin, only hemoglobin showed a statistically significant rise during the convulsive seizure, rising from a mean of 12.7 gm./100 cc. (10.7–14.7) for the controls to a mean of 15.7 gm./100 cc. (13.6–18.3) for the hexafluorodiethyl ether-exposed rats. The standard deviations for the control and experimental groups were 2.25 and 1.79 respectively, while the p values were 0.05–0.02. The control value of the white cell count was a mean of 8,080 (5,300 to 11,000), while the hexafluorodiethyl ether-treated group showed a mean of 16,070 (9,950 to 33,150). The p value was 0.10. The red cell count of the control group gave a mean of 6,831,000 (6,040,000 to 7,730,000), while the experimental group had a mean red cell count of 8,142,500 (6,910,000 to 10,015,000). The p values were 0.10–0.05.

(10) EFFECT OF HEXAFLUORODIETHYL ETHER ON MUCOUS MEMBRANES

Two percent v.v. solutions of hexafluorodiethyl ether and ethyl ether in corn oil were prepared. Two drops of hexafluorodiethyl ether solution were instilled into the conjunctival sac of 4 rabbits. For comparative purposes the ethyl ether solution was used in the other eye. The conjunctivae and lid margins were examined immediately and at intervals of 15 minutes during one hour. Mild chemosis was present in all eyes for about 45 minutes. Hexafluorodiethyl ether appeared by this procedure no more irritating than ethyl ether. After 24 hours no visible effects of either agent were discernible.

(11) HEXAFLUORODIETHYL ETHER AND CHOLINESTERASE

Two dogs weighing approximately 8 kgm. were anesthetized with ether and prepared for blood pressure recording from the carotid artery. In each animal 1 cc. of

acetylcholine chloride solution, 1 in 10^5, was injected intravenously and the depressor response of 52 mm. was recorded. Specimens of serum from each animal were incubated for one hour with (1) the acetylcholine solution, (2) acetylcholine solution plus 1 mgm. prostigmine, (3) acetylcholine solution plus 0.7, 1.4 and 2.8 mgm., respectively, of hexafluorodiethyl ether. After incubation, the solutions were injected into the respective animals. The acetylcholine solution with serum was completely hydrolyzed with no depressor response. The acetylcholine solution with serum and prostigmine showed no diminution in depressor activity. In the three concentrations of hexafluorodiethyl ether cholinesterase was not affected in vitro, as shown by the complete absence of the depressor response of the acetylcholine solutions upon injection. These studies indicate that the convulsive syndrome elicited by hexafluorodiethyl ether is not mediated by excessive acetylcholine activity.

(12) POSSIBLE HYPOGLYCEMIC ACTION

One rabbit weighing 2.5 kgm. with a blood sugar of 148 mgm. percent was given 5 cc. of 10 percent dextrose solution intravenously. The animal was then exposed to the vapor of hexafluorodiethyl ether (0.25 cc. in a 10-liter jar). The convulsive syndrome occurred within 1 minute, indicating the failure to protect by a plethora of glucose in the blood. Blood sugar levels on 5 additional rabbits were 118, 120, 146, 134 and 139 mgm. percent. They were exposed to hexafluorodiethyl ether according to the foregoing description. During the convulsive syndrome, blood sugar levels were 143, 151, 155, 164, and 174 mgm. percent respectively. These data indicate that hypoglycemia is not a factor in the seizure syndrome. The mild hyperglycemia is probably of adrenal origin.

(13) EFFECT ON CEREBRAL METABOLISM

(a) Three rats were subjected to the convulsive action of hexafluorodiethyl ether and killed by decapitation immediately following the seizure. The oxygen uptake of the homogenized brain tissue was determined by the Warburg technique using brain from untreated animals as control. The QO_2 values were 4.6, 4.9, 4.9, 4.6, 4.5 and 5.0; mean 4.7. These data indicate that a single exposure to hexafluorodiethyl ether did not affect the gaseous metabolism of the brain when determined immediately after the seizure.

Owing to the insolubility of hexafluorodiethyl ether in water, in vitro tissue studies were difficult to carry out. However, suspending the hexafluorodiethyl ether in 10 percent Polysorbate–80 (which itself produced marked depression of the oxygen uptake of brain tissue) a depression of oxygen uptake of only 8 percent was observed in concentrations of 60 and 75 mgm. percent. The effect of the added hexafluorodiethyl ether was considered negligible.

(b) To avoid any influence of respiratory movement upon the cerebral A–V oxygen difference, 4 dogs, anesthetized with Pentothal sodium and paralyzed by a slow, continuous intravenous drip of 0.2 percent succinylcholine chloride, were provided with artificial respiration throughout the experiment. Control blood samples were taken from the carotid artery and internal jugular vein. Hexafluorodiethyl ether (0.25 cc.) was then aspirated into the tracheal cannula, and the cerebral cortical dysrhythmia observed by EEG activity. Blood samples (arterial and venous) were taken during maximal seizures and during the recovery phase. All samples were analyzed by the Van Slyke-Neil technique. The data in Table IV show a pronounced fall in A–V oxygen difference following the inhalation of hexafluorodiethyl ether. This decrease would suggest an increased level of oxygen consumption in the cerebral cortex during convulsion.

TABLE IV.—CEREBAL A-V OXYGEN DIFFERENCE (VOL. PERCENT)

	Control	5 min. after hexafluorodiethyl ether (convulsion)	15 min. after recovery
Dog No.:			
1	5.82	3.87	----------
2	5.62	1.91 and 1.88	----------
3	6.23	2.23	3.66
4	6.76	2.73	2.78

The outstanding advantage or value of hexafluorodiethyl ether as a convulsive agent does not reside solely in its strong convulsant action, but also involves its ability to produce a convulsive shock having a beneficial therapeutic effect, particularly for the treatment of mental disorders in humans. Thus, as noted above, the agent is characterized by the provocation of a cortical response closely simulating that of pentamethylenetetrazole and electroshock, now employed as convulsant stimuli for mental therapy. The administration of hexafluorodiethyl ether to mentally ill patients has shown it to have a beneficial therapeutic effect similar to and sometimes more favorable than would be expected by pentamethylenetetrazole or electroshock therapy.

Hexafluorodiethyl ether may be administered advantageously in vapor form by inhalation. In this method of administration, the vapor is admixed with a suitable, pharmaceutically acceptable gaseous vehicle, or carrier, such as oxygen or air, the mixture then being presented in any suitable manner to permit its inhalation by the patient. The gaseous carrier preferably contains at least a life-sustaining amount of oxygen, i.e.; about 20 percent, since the patient thereby will receive oxygen right up until the cessation of administration, when temporary cessation of respiration usually supervenes. Other respirable gases, however, may be used as a carrier, for example, helium, nitrogen, and/or nitrous oxide, although in each case it is preferred that oxygen or air be admixed therewith in an amount at least sufficient for normal respiratory purposes, thereby to avoid hypoxia or reduce it to an unobjectionable degree during the interval of the patient's respiratory lapse.

Apparatus of the type suitable for the administration of inhalant type medicants or anesthetics may be used to administer hexafluorodiethyl ether. Preferably, such apparatus embodies a means for volatilizing the liquid agent in a confined chamber and conveying the vapors together with the carrier gas to the patient upon inhalation. One such device, for example, may be in the form of a mask inhaler having, connected to an inhalation passage, a chamber communicating with the atmosphere and containing a porous member adapted to retain a quantity of the liquid agent. Thus, upon inhalation, air is drawn into the chamber, admixed with the hexafluorodiethyl ether vapor, and thence delivered to the patient. Such a device preferably incorporates a check valve means in the inhalation conduit and a separate exhalation port such that the patient's exhalation is not discharged through the vaporizing chamber. In such a device, the amount of the agent administered may be controlled by the amount placed in the vaporizing chamber and the length of time that the patient is permitted to inhale the vapors. It will be apparent, of course, that a greater precision of control might be obtained with further refinements in the administering apparatus, such as the provision of valve means and the like, which are well known expedients. It is also preferred that the patient's exhalation be vented through a suitable adsorbent, such as a charcoal filter, to trap any trace amounts of the agent that might not have been taken up by the patient during breathing.

Advantageously, the response of the patient to hexafluorodiethyl ether is extremely rapid. Accordingly, the method of convulsive shock treatment of the present invention may be carried out readily by administering the

agent progressively until the prescribed symptoms are observed corresponding to the condition at which no further administration is desired. Thus, for example, to carry out a convulsive shock treatment by inhalant administration the patient, generally, is permitted to inhale the vapors until he loses consciousness and there is the onset of convulsion, at which point further administration of the agent is discontinued. Usually, just prior to the convulsion the patient exhibits blinking of the eyelids, nystagmus and fasiculations of the muscles of the face. When the confined vapors, vaporized at atmosphoric temperature, are inhaled in admixture with air at a concentration of about 1%, by volume, these effects may occur within 20 to 30 seconds, although some variations have been found between patients, particularly those differing substantially in size and weight. Larger, or heavier, patients have a greater tidal volume and thus take in a greater amount of the convulsive agent within a shorter time than smaller patients. Generally, a dosage of about 500 to 1000 mg., and preferably not more than about 3000 mg., are effective to provide the desired convulsive seizure and corresponding cortical dysrhythmia, for a single convulsive treatment.

The onset of the convulsion in the patient, following the administration of hexafluorodiethyl ether, without muscle relaxants and/or thio barbiturates, is signalled in the typical seizure by an initial increase in respiratory depth followed by unconsciousness and a short sequence, of a few seconds duration, of myoclonic jerks of the limbs. A typical grand mal convulsive seizure then ensues, characterized by a tonic phase of extensor rigidity with opisthotonus and apnea, lasting from 15 to 30 seconds, and a subsequent clonic phase of jerking movement which gradually overtakes the patient and lasts, usually, from 15 to 35 seconds. Occasional clonic jerks may occur within the next minute. Thus, the convulsive seizure, when the administration of the agent is discontinued at about the onset of the convulsion, lasts for about one minute and is characteristic of the pattern of a grand mal seizure such as is evoked by Metrazol (pentamethylenetetrazole) and electroshock convulsive treatments and in spontaneous grand mal epileptic seizures. The period of apnea occurring during the convulsive seizure appears somewhat diminished when contrasted with the period of apnea occurring in convulsive seizures produced by other means such as pentamethylenetetrazole and electroshock. Following the clonic phase, unconsciousness usually prevails from 5 to 10 minutes. Within 15 to 20 minutes after the seizure the patients are found to be capable of walking without difficulty and to be mentally clear.

It is apparent that the concentration of the vapors of the hexafluorodiethyl ether in the inhalant composition will affect the rapidity of the onset of the desired response. Generally, it is desired that its concentration not exceed an amount which would be objectionable or unduly irritating to the patient such as might render the mixture nonrespirable. On the other hand, the concentration is preferably sufficiently high to produce the convulsive response within as short a period as possible. Concentrations of about 20 p.p.m. to 30 p.p.m. w./v., corresponding to 0.3 to 1% v./v., have been found to be tolerated readily by the patient and to provoke the convulsive response within a sufficiently short period. Significantly, it has been found that patients have a complete amnesia with respect to the convulsive seizure itself. Since the period of response following administration of hexafluorodiethyl ether is very small and the onset of the convulsion is relatively smooth, the patients have relatively little apprehension to this form of treatment.

The therapeutic use of hexafluorodiethyl ether as described above involves the administration of a threshold dosage capable of provoking in a patient convulsive seizures of the above-described grand mal proportions. Generally, it is believed, based upon previous investigations and results of pharmacologic and electroshock treatments, that the administration or applicaton of the stimulating agent of at least the threshold amount, sufficient to provoke such seizures, is most effective for imparting beneficial therapeutic effects as a means of treating metal disorders. While the seizure pattern, elicited by the agent, manifests a sufficient dosage, the stimulus applied to the brain is believed to be the source of the beneficial influence of the treatment. Accordingly, it may be possible, as has been suggested in connection with the usual Metrazol or electroshock treatment, to administer a dosage of the convulsive agent sufficient to stimulate the cortical motor system in a manner corresponding to that normally accompanied by a major seizure pattern, but in which the manifested seizures are obliterated or reduced by sedation of the patient such as with thio barbiturates and/or muscle relaxants. In such cases, the administration of the convulsive agent would preferably be based upon other suitable responses unaffected by the sedation such as EEG, or by direct quantitative dosage administration.

There has also been proposed in connection with convulsive therapy employing electroshock, the use of subconvulsive treatments. Such subconvulsive response may be described as petit mal, analogous to the corresponding phenomenon in epilepsy and is essentially characterized by mere unconsciousness accompanied by apnea. This response is not considered to have any therapeutic effect in mental disorders comparable to that obtained at the level of generalized convulsive seizures. However, such treatment has been found in same instances to be valuable in the manic phase of manic-depressive psychoses and for the manic symptoms of other periodic psychoses owing to its calming effect. The petit mal response has no parallel in pentamethylenetetrazole treatment where unconsciousness does not occur if the injection does not lead to a convulsion. Owing to the dreaded feeling of apprehension experienced by the patient in subconvulsive response to pentamethylenetetrazole, such treatments are not employed. While the extent of therapeutic benefit has not been determined in subconvulsive response with hexafluorodiethyl ether, this agent is not characterized by producing such feelings of apprehension in the patient and might be employed where such response is deemed desirable. Such response has been obtained by administering concentrations of the agent in the order of about 0.1 to 0.2 percent v./v., for subconvulsive dosages of about 70 to 300 mg.

When such amounts of the agent have been administered the patient becomes unconscious. Clonic jerks may be manifested in the extremities or facial muscles. Pupillary dilitation and nylstagmus occurs with rapid upper lid blinking. This may occur with or without vocalization.

As mentioned above, a unique method by which hexafluorodiethyl ether may be administered advantageously is by inhalation. This agent provides, by such administration, desirable ease of control of the depth and duration of the convulsive seizure. A significant advantage of this mode of administration is the self-regulation it affords as to the dosage of the agent. It will be seen that with the occurrence of apnea at the commencement of the convulsive seizure the patient will not receive further amounts of the agent by voluntary respiration, thus avoiding inadvertent overdosage. However, the agent has been administered in pharmacological experiments both intravenously and intramuscularly in suitable pharmaceutical vehicles. For intravenous or intramuscular administration, a vehicle such as one of the polyethylene glycols in aqueous solution may be used. Suitable pharmaceutical vehicles which are compatible with the elements of blood and miscible with blood and hexafluorodiethyl ether, and which are inert with respect to hexafluorodiethyl ether and which will form an injectable composition with hexafluorodiethyl ether that is miscible and compatible with

blood, may be selected from those commonly used in such methods of administration with other drugs.

Hexafluorodiethyl ether may be administered with particular advantage intravenously in the form of a sterile injectable aqueous composition, including a vehicle such as one of the polyethylene glycols which is effective to solubilize the hexafluorodiethyl ether in the aqueous medium. Carbowax 300, for example, which is a trademark identifying a particular brand of a polyethylene glycol having an average molecular weight of approximately 300, is particularly suitable. In suitable proportions, the polyethylene glycol is effective to render the hexafluorodiethyl ether soluble in water, thus forming a readily injectable composition. However, it is desirable to use no more than the amount of the polyethylene glycol that is required to form a water solution of the hexafluorodiethyl ether. For example, a composition containing about 5% v./v. hexafluorodiethyl ether, 76% v./v. Carbowax 300 and the balance water forms a highly satisfactory injectable solution. The composition is stable and readily sterilized by autoclaving at elevated pressure such as, for example, 15 p.s.i. for about 25 minutes.

The amount of the polyethylene glycol that will effectively solubilize the hexafluorodiethyl ether in water may be decreased by the use of a small amount of ethyl alcohol. Thus, for example, a mixture of 5% v./v. hexafluorodiethyl ether, 55% Carbowax 300, 15% ethyl alcohol (95%) and the balance water forms a highly desirable injectable solution which is further enhanced by being less viscid and more easily injected. Such solution also is readily sterilized by the autoclaving. In aqueous solution with polyethylene glycol, concentrations of about 3–7% v./v. hexafluorodiethyl ether appear to include the most advantageous mixtures. However, it is generally desirable to employ the maximum concentration of hexafluorodiethyl ether in the injectable composition that will also permit retention of suitable fluidity for injection and desired compatibility with the blood stream. Generally, small amounts of ethyl alcohol of up to about 20% v./v. will be effective in affording a suitable aqueous solution of hexafluorodiethyl ether in these concentrations with a polyethylene glycol such as Carbowax 300.

In administering hexafluorodiethyl ether intravenously such as above, substantially the same dosages are effective as have been described in connection with inhalant administration. It is desirable, however, to ascertain the desired dosage for each patient in general relation to his weight in accordance with the principles conventionally followed for the administration intravenously of anesthetic and many other pharmacologic agents. In general, the convulsive dosage of hexafluorodiethyl ether corresponds to about 8–15 mg./kg. of the subject's weight. The techniques for such mode of administration is, of course, readily understood to those skilled in the art having the requisite professional training. It may be stated, however, as illustrative, that the administration of such dosage level reliably produces the typical seizure within about 20–30 seconds. Following the typical seizure pattern recovery occurs within 5–10 minutes.

In general, the types of mental illness for which convulsive therapy as herein described with hexafluorodiethyl ether is suited are those for which electroshock and/or Metrazol convulsive therapy have been found, or are considered, beneficial. Such types of mental illnesses include involutional depressions, depressed state of manic psychoses, and acute and chronic schizophrenic reactions. Such treatments with hexafluorodiethyl ether are also effective for maintenance treatment in chronically disturbed schizophrenics.

The following examples illustrate the application of this agent, according to the methods herein described, in convulsive therapy for treating mentally ill patients. In the following clinical cases, the patients received a dosage of from 500 to 1000 mg. of hexafluorodiethyl ether, for each single convulsive treatment.

Case 1

A thirty-four year old married female with a diagnosis of psychotic depressive reaction manifested by crying spells, progressive inability to care for her children, house or her person, increasing isolation associated with increasing agitation who had had no previous psychiatric hospitalization prior to the present time, was started on a course of treatment with hexafluorodiethyl ether. This was administered by placing three cc. of the liquid agent in a plastic inhaler disbursed on cotton. This inhaler was of the type employed for the administration of the generally used nasal decongestants and comprised essentially a vaporizing chamber for holding the liquid agent on a cotton wick, the chamber being open to the atmosphere to permit air to be drawn therein upon inhalation and having a protruding tubular portion adapted to be inserted into the patient's nostril. During the later series of administrations a face mask of the type hereinbefore described was employed for the more effective administration of the gaseous vapor.

The only premedication employed was atropine sulphate which is a customary medicament given prior to the administration of any form of convulsive therapy in order to dry the salivary secretion.

The patient received a total of five treatments with hexafluorodiethyl ether. In each treatment upon the commencement of inhalation a convulsive seizure ensued within ten to twenty seconds, at which time the inhaler was removed. The seizure episode resembled that of electroshock therapy and continued for a period of approximately forty to sixty seconds. Unconsciousness intervened from the onset of the convulsion and continued thereafter for from four to seven minutes. Upon returning to consciousness the patient had no specific complaints and no untoward reactions were observed during any of the treatments to which the patient was subjected, and in each case a more gradual introduction of the convulsion was observed as compared to that obtained in an electro-convulsive treatment.

After an initial course of six treatments extending over a period of two weeks, the clinical reports on this patient stated that she was doing much better, was participating in ward activities, her inaccessibility appeared resolved and she seemed to get along well with ward personnel. She expressed increasing desires to go home and be with her family. She seemed much more relaxed and comfortable. Two days after her last treatment she was discharged from the hospital and when called back to the hospital three weeks later for an interview she was doing extremely well. She was taking care of her family, routine household duties, and appeared to be in excellent spirits.

Case 2

A twenty-nine year old married white female with a diagnosis of schizophrenic reaction, catatonic type, manifested by disorientation, agitation, preoccupation overactivity, autistic mannerisms and extreme sensitivity to any type of excitement with resulting episodes of confusion and uncooperativeness, was admitted to the hospital for a second time, a year after her first admission.

The medication, hexafluorodiethyl ether, was administered through an inhalation mask, as hereinbefore described, and was given for a total of twelve treatments over a four-week period. The premedication employed was atropine sulphate. In each treatment upon the commencement of inhalation through the mask vaporizer a convulsive seizure ensued within ten to forty seconds, at which time the inhaler was removed. The seizure episode resembled that of an electroshock therapy and continued for a period of approximately forty to sixty seconds. Unconsciousness intervened from the onset of

the convulsion and continued thereafter from four to seven minutes. Upon returning to consciousness the patient occasionally complained of a slight headache which quickly cleared up. No untoward reactions were observed. In each of the treatments to which the patient was subjected a more gradual introduction of the convulsion seizure was observed than that which would have been obtained with electroconvulsive therapy.

This patient as a result of the treatment became more integrated, less excitable; her overactivity stopped; she started relating in a friendly manner to the other patients, and lost her autistic mannerisms. She made an excellent ward adjustment and appeared to be much more relaxed and comfortable. In interviews with this patient she expressed here preference for this type of treatment, namely, hexafluorodiethyl ether, as compared with electroconvulsive therapy which she had had in her previous hospital admission. She felt that she was not as frightened of this treatment as she was of electroshock, which she dreaded since she felt it "burned her brain." The patient also stated that she did not feel as confused nor did she have as much trouble with her memory with this method of treatment as she recalled with electroconvulsive therapy. Three weeks after she had her last treatment with hexafluorodiethyl ether she was discharged from the hospital as markedly improved.

Case 3

A thirty-one year old white female was admitted to this hospital with a diagnosis of schizophrenic reaction, chronic, undifferentiated type, manifested by auditory and visual hallucinations, posturing and ritualistic mannerisms, flattened effect and disorientation. Prior to her admission she had been seen in the outpatient clinic for outpatient treatment because of a previous admission to this hospital, but as she became more disturbed had to be readmitted.

She was given a course of twelve treatments with hexafluorodiethyl ether over a four-week period according to the same procedure as outlined above and with the same results as indicated in the first and second cases. Two weeks after her last treatment she was discharged from the hospital. Her psychotic behavior had been resolved and she was making an excellent adjustment at home.

While the administration of hexafluorodiethyl ether to provoke a conculsive state in patients has been described herein primarily as a useful element in the treatment of mental disorders, it is believed that the convulsive response to this agent may be put to use for other purposes. For example, hexafluorodiethyl ether may be administered to suspected epileptic patients to detect epileptogenic foci in the brain area by precipitating a cortical convulsive response.

This parallels the use of Metrazol in subconvulsive doses for the detection of epileptogenic foci in the brains of individuals suspected of subclinical epilesy. This is achieved, as a rule, buy a study of the electroencephalographic pattern of the patient upon the injection of 100–300 mg. of Metrazol intravenously. Hexafluorodiethyl ether may be used effectively to serve the same function such as by permitting the suspected individual to inhale a concentration of about 0.1 to 0.2% by volume and studying the electroencephalographic pattern. The administration of small amounts of hexafluorodiethyl ether for this purpose may be accomplished in a highly advantageous manner by intravenous injection. Thus, for example, a composition consisting of 5% v./v. hexafluorodiethyl ether, 76% v./v. Carbowax 300 and the balance water intravenously injected in dosages of about 1–1.5 cc. have been found highly effective and dependable for this purpose. Other suitable, injectable compositions such as herein above described may also be used. Such dosages represent subconvulsive dosages of at least about 70 mg. of the agent which are generally satisfactory for detecting subclinical epileptogenic foci. The theoretical consideration underlying this use of the agent is that in persons whose brains have epileptogenic foci, such dosages show a convulsive electroencephalographic pattern or other significant pattern with subthreshold concentrations owing to a greater cerebral sensitivity.

It is believed that the compound hexafluorodiethyl ether has never previously been synthesized. It has been prepared in accordance with the present invention by the reaction of 2,2,2-trifluoroethyl paratoluenesulfonate with an alkali metal 2,2,2-trifluoroethanolate, advantageously under anhydrous conditions. Sodium trifluoroethanolate is the preferred reactant. However, potassium and lithium trifluoroethanolate also may be used. The reaction proceeds most advantageously at temperatures above 150° C. and particularly at temperatures in the range of 150° to 170° C. The method may be carried out at atmospheric pressure or at superatmospheric pressures, for example, pressures of about 160 to 200 p.s.i. A suitable inert solvent such as trifluoroethanol or ethyl ether is employed, trifluoroethanol being the preferred solvent. In carrying out the reaction at atmospheric pressure, the reaction mixture, advantageously, is dispersed in a dispersing medium having a relatively high boiling point, such as mineral oil, xylene or silicone oil. One advantage of the atmospheric pressure method is its adaptability to a continuous phase reaction. As an illustration of one manner of advantageously carrying out this process, an excess of 2,2,2-trifluoroethanol is treated with sodium metal to which is then added trifluoroethyl p-toluene-sulfonate. The resulting mixture is heated to about 150° to 160° C. and maintained under a pressure of from 160 to 200 p.s.i.

The time of the reaction may vary and will depend to a great extent, of course, upon the conditions of temperature and pressure employed. Generally, the reaction may reach completion anywhere between 5 to 24 hours and about 15 hours under the preferred operating conditions.

The molar ratio of the reactants may be varied within wide limit without materially affecting the reaction. However, molar ratios of about 0.8:1 to 1.2:1 of trifluoroethyl p-toluene sulfonate to alkali metal trifluoroethanolate, give suitable yields.

On completion of the reaction, the product may be separated or isolated by conventional procedures, e.g. by distillation, extraction, etc., although distillation has been found highly advantageous. The crude product thus obtained is then advantageously washed with aqueous alkaline solution such as dilute potassium hydroxide, followed by filtration and distillation to give the final substantially pure hexafluorodiethyl ether free of objectionable toxic impurities.

The following example illustrates the preparation of hexafluorodiethyl ether:

A reaction mixture of 16 g. (0.7 M) of sodium with 400 ml. (5.6 M) of trifluoroethanol was loaded into a 2 liter Aminco Rocking Bomb with 163 g. (0.62 M) of trifluoroethyl p-toluene sulfonate. The sealed bomb was rocked and heated at 150° C. for hours at 150–160 p.s.i. The cooled contents of the bomb were filtered to separate a light brown solid precipitate. The brown filtrate was distilled through a fractionating column and 75.5 g. of a fraction B.P. 60–68° C. were collected, representing 64% of the theoretical yield. This crude product was purified by washing two times with 5 N KOH followed by drying over 10 g. of KOH pellets. Filtration and distillation through a 105 plate column gave a 52.8 g. center fraction of pure hexafluorodiethyl ether, B.P. 63.9° C./760 mm; n_D^{20} 1.2797.

Analysis.—Calculated for $C_4H_4F_6O$: C, 26.38%; H, 2.21%; F, 62.60%. Found: C, 26.30%; H, 2.19%; F, 62.39%.

We claim:

1. In convulsive therapy the method of treating a patient with hexafluorodiethyl ether which comprises administering to said patient a dosage of 70–3000 mg. of said hexafluorodiethyl ether.

2. In convulsive therapy the method which comprises administering internally a dosage of about 500 to 1000 mg. of hexafluorodiethyl ether to a patient.

3. The method of convulsive therapy which comprises administering internally hexafluorodiethyl ether to a human patient so as to produce a concentration of said ether in the blood stream of said patient sufficient to evoke a convulsive response.

4. The method according to claim 3 wherein said hexafluorodiethyl ether is administered in vapor form by inhalation.

5. The method according to claim 4, wherein said hexafluorodiethyl ether is administered by inhalation induced by means of forced respiration while said subject is under the influence of a relaxant.

6. The method of convulsive therapy according to claim 3 wherein said administration of hexafluorodiethyl ether is accompanied by sedation and reduction of muscular response to thereby minimize the seizures normally manifested by the patient.

7. The method of convulsive therapy which comprises administering by inhalation to a human patient a respirable composition comprising essentially oxygen and hexafluorodiethyl ether, until said patient loses consciousness and there is the onset of convulsions.

8. In convulsive therapy the method which comprises administering to a living being by inhalation a respirable composition containing at least a 0.1% by volume concentration of hexafluorodiethyl ether.

9. In convulsive therapy the method of treating a living subject by producing in said subject a convulsive response which comprises administering internally to said subject, by parenteral administration, an effective dosage of hexafluorodiethyl ether in a suitable fluid pharmaceutical carrier.

10. The method of treating mental illness in human patients which comprises administering to said patients internally an effective amount of the agent hexafluorodiethyl ether.

11. A physiologically active, respirable, inhalant composition comprising an effective amount of hexafluorodiethyl ether in vapor form in admixture with a respirable gaseous carrier.

12. A composition according to claim 11 containing at least about 20 percent oxygen.

13. A pharmaceutically useful injectable composition adapted to be administered internally to living subjects, characterized by physiological activity as a strong convulsant comprising an effective amount of hexafluorodiethyl ether and a physiologically suitable injectable carrier.

14. A pharmaceutical useful composition in accordance with claim 13, wherein said vehicle includes a polyethylene glycol.

15. A composition according to claim 13 in dosage unit form for producing a convulsive response in a living subject, comprising from about 150–1000 mg. of hexafluorodiethyl ether and a pharmaceutical carrier.

16. An injectable pharmaceutical composition effective for use in the production of convulsive response in living subjects, comprising an effective amount of hexafluorodiethyl ether and an aqueous pharmaceutical vehicle.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,483,298 Dated December 9, 1969

Inventor(s) John C. Krantz, Jr. and Louise S. Croix

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 5, line 54, the word "absorber" should be -- adsorber --

Col. 6, line 10, the word "tremore" should be -- tremors --

Col. 6, line 31, the word "does" should be -- dose --

Col. 6, line 34, the word "the" should be -- two --

Col. 7, line 68, the word "conculsive" should be -- convulsive

Col. 12, line 30, the word "same" should be -- some --

Col. 12, line 51, the word "nylstagmus" should be -- nystagmus

Col. 12, line 51, the word "occurs" should be -- occur --

Col. 13, line 54, the word "techniques" should be -- technique

Col. 15, line 15, the word "here" should be -- her --

Col. 15, line 59, the word "buy" should be -- by --

Col. 16, line 61, insert -- 15 -- after the word "for"

Col. 18, line 19, the word "pharmaceutical" should be -- pharmaceutically --

SIGNED AND SEALED SEP 8 - 1970

(SEAL)
Attest:

Edward M. Fletcher, Jr.
Attesting Officer

WILLIAM E. SCHUYLER, JR
Commissioner of Patents