Clinical and Laboratory Evaluation of a New Inhalation Agent: Compound 347 $(CHF_2\text{-}O\text{-}CF_2\text{-}CHF\ Cl)$

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Compound 347 ($CHF_2\text{-}O\text{-}CF_2\text{-}CHFCl$), a new non-explosive, fluorinated ether, was administered with nitrous oxide–oxygen to 100 patients for major elective abdominal operations. This agent provided rapid, pleasant induction and emergence and adequate hypnosis, analgesia and muscular relaxation, with minimal alterations in the vital signs. Circulatory dynamics and cardiac rhythm remained relatively stable. Patient acceptance was excellent. Comprehensive laboratory studies of the blood showed no change in acid-base balance, serum sodium and chloride, a slight decrease of serum potassium and inorganic phosphorus, a marked increase in blood glucose and plasma cortisol, no change in histamine or serotonin, and an increase in plasma catecholamines. Transaminases (SGOT and SGPT) rose slightly, while there was no change in the blood urea nitrogen or creatinine. This anesthetic appears to deserve clinical evaluation.

RECENTLY, a new halogenated liquid, 2 chloro-1,1,2 trifluoroethyl difluoromethylether (CHF_2-O-CF_2CHFCl) was developed. Designated Compound 347,†† this compound is a potent

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anesthetic, safe in animals and non-explosive in anesthetic concentrations.[1] Virtue et al. verified its anesthetic properties in animals and found that it was incompatible with epinephrine and that it appeared to excite the neuromuscular system during deep anesthesia.[2] Their report contained an evaluation of effects in dogs and preliminary tests in non-operated volunteers and a few patients. They felt that this compound might be worth clinical evaluation.

Compound 347 is related to both halothane and methoxyflurane although it is more stable than either. Table 1 compares the properties of fluorinated anesthetics in current use with those of Compound 347.†† Physical data about the new compound were provided by Ohio Medical Products and Dr. E. I. Eger.

The following effects have been described for the compound: minimal stimulation of salivary secretions and bronchomotor tone; moderate stimulation of respiratory rate and slight depression of tidal volume; progressive depression of blood pressure with increasing anesthetic depth; absence of myocardial irritability unless epinephrine is administered. It appears to provide moderate muscular relaxation and analgesia similar to that produced by methoxyflurane, fluroxene and diethyl ether.[1, 2]

This report deals with evaluation of Compound 347 in 100 selected patients who underwent major elective abdominal operations. A concurrent study of methoxyflurane (Penthrane®) was carried out to compare the two anesthetics with respect to the amount of anesthetic utilized, rate of recovery from anesthesia, and incidence of nausea and vomiting, and to determine whether either agent has a

TABLE 1. Characteristics of Fluorinated Anesthetics

	Fluroxene	Halothane	Methoxyflurane	Compound 347
Structural Formula	CF_3CH_2—O—CH=CH_2	$CF_3CHBrCl$	CH_3—O—CF_2CHCl_2	CHF_2—O—CF_2CHFCl
Molecular Weight	126	197	164	184
Boiling Point	43.2	50.2	104.7	56.5
Vapor Density (Air = 1)	4.4	6.9	5.7	6.4
Vapor Pressure (20° C., mm.Hg)	286	241	23	180
Odor	ethereal (pleasant)	sweet (pleasant)	fruity (pleasant)	ethereal (pleasant)
Flammability (<5% concentration)	Yes	No	No	No
Stability				
Soda lime	Yes	Yes	Yes	Yes
Metals	Yes	No	Yes	Yes
Na methoxide in CH_3OH	No	No	No	Yes
Light (UV)	No	No	No	Yes
Stabilizer required	Yes	Yes	Yes	No
Partition Coefficients:				
Water/gas at 37° C.	0.51	0.74	4.5	0.78
Blood/gas at 37° C.	1.37	2.36	13.0	1.91
Oil/gas at 37° C.	47.7	224	885	98.5
Oil/water distr. coeff.	94	330	400	130
Hypnotic Potency (Diethyl ether = 1)	1.5	5	6	3
Analgesic Potency (Diethyl ether = 4)	4	1	4	3(?)
Relaxant Potency (Diethyl ether = 4)	3	1	4	3
Vapor Concentration (%) for Surgical Anesthesia				
Induction	3–8	2–4	2–4	2–5
Maintenance Air-SR	3–6	1.5–3	1–3	2–4
$N_2O:O_2(6:4)$ CR	<5	<2	<1.5	<3
Concentration in Blood during Surgical Anesthesia (mg/100 ml)	20–40	10–20	10–25	15–25

persistent analgesic effect during the first six hours of the recovery period.

Materials and Methods

A signed informed consent for the study was obtained from each patient. Premedication was atropine (0.4 to 0.6 mg.) alone or with a hypnotic (secobarbital 100 mg or diazepam 20 mg.). A few patients were given 25 mg. meperidine (Demerol®) to allay discomfort during insertion of catheters into blood vessels. Gallamine (60 to 120 mg.) and thiopental 2.5 per cent (200 to 400 mg.) were given intravenously for induction and, after oxygenation, an orotracheal tube was inserted. Maintenance was accomplished with Compound 347 (< 3 per cent) and nitrous oxide–oxygen (60:40) in a semiclosed system using a calibrated Fluotec vaporizer outside the circle-absorption system. The Fluotec vaporizer scale read approximately 25 per cent higher than the delivered vapor concentration. Supplementary doses of gallamine were given but, in all cases, we attempted to rely on the anesthetic vapor and nitrous oxide to provide satisfactory surgical conditions. Pulmonary ventilation was controlled with a mechanical ventilator. When skin closure was begun,

breathing was controlled or assisted manually until spontaneous breathing appeared effective. Tidal volume and airway pressure were recorded. Respiration was controlled at a rate of 16 to 20 per minute and minute volume usually was set at approximately twice the Radford Nomogram value. Ringer's lactate solution, 0.9 per cent saline solution, and whole blood were administered as necessary. Dextrose 5 per cent in water was given in the first 20 cases only.

Auscultatory blood pressure and pulse rate were recorded at least every five minutes. Rectal temperature was monitored with a thermister probe. Urinary output was recorded in patients who had bladder catheters by gravity drainage into a calibrated trap bottle. Lead II of the electrocardiogram was monitored on an oscilloscope and serial tracings were made on a direct writer before and during induction and intubation, and at intervals thereafter. Postoperatively, respiratory rate and minute volume were measured with a Wright respirometer at intervals up to one hour, or longer if the patient had not recovered. Wakefulness was determined by noting the times when the patient first opened his eyes and protruded his tongue on command.

Arterial blood samples were taken and analyzed the day before surgery (or prior to premedication), one hour after premedication, at one-hour intervals during operation, as soon as operation was completed (while breathing oxygen), then 30 minutes, 60 minutes, and 24 hours after operation. Analyses were carried out with an Epsco Medical Blood Parameter Analyzer with a constant temperature bath at 37° C., a Metrohm pH electrode, a Clark platinum-membrane-covered electrode for measuring oxygen tension, and a carbon dioxide tension (Severinghaus) electrode. Oxyhemoglobin saturation (Sa_{O_2}) was measured with a Reflection Oximeter Model 10,800 (American Optical Co.) with a reproducibility of ±0.5 per cent in the 85 to 100 per cent range. Hematocrit was measured by a micromethod and plasma bicarbonate concentration was estimated from pH and Pa_{CO_2} values using a line chart.[3] Hemoglobin concentration was determined with cyanmethemoglobin standard solutions. Oxygen content in volumes per 100 ml. was calculated from the product of the hemoglobin Gm./100 ml. × oxygen saturation × 0.0139.[4]

Cardiac output determinations were performed on 11 patients using a Gilford Densitometer 123-IR, a Lexington Instrument Computer, a Texas Instrument Two-channel Recorder and a Gilford Constant Flow System 150-S. A Sanborn 8-channel Cathode Ray Oscillograph, No. 768-100 was used to monitor systemic pulmonary artery and central venous pressures with Statham strain-gauge transducers.

Either a catheter was placed in the left brachial artery by the Seldinger technique[5] or an arterial cutdown was performed in each patient. The superior vena cava was cannulated percutaneously through the subclavian vein by the infraclavicular approach. In some instances, a small catheter was threaded through the right atrium and ventricle into the pulmonary artery.

The densitometer was calibrated with indocyanine green dye mixed with the patient's blood, and the computer was balanced.[6, 7] Arterial blood was withdrawn at a constant speed from the brachial artery through a sterile cuvette in the densitometer. A 5 mg. dose

of dye was injected into the superior vena cava and flushed with 10 ml. of heparinized saline. The cardiac output was read as a deflection from the baseline and compared to the deflection after a known amount of dye. Blood was reinfused into the patient. The following formula was used:

$$\text{cardiac output} = \frac{3.90 \times \text{deflection standard}}{\text{deflection of patient}}$$

The result was read as output in liters per minute. The actual dye-dilution curve was imprinted also and was a check of the validity of the determination.

Cardiac outputs were performed in duplicate before anesthesia, immediately after intubation, and at approximately half-hourly intervals after the start of anesthesia with Compound 347; at the end of anesthesia, and then one-half hour and one hour later in the recovery ward.

The following circulatory parameters were calculated for the times corresponding to the serial cardiac output estimations:

Cardiac index (CI)

$$= \frac{\text{cardiac output (liters/min.)}}{\text{body surface area}}$$

Stroke volume (SV)

$$= \frac{\text{cardiac output (liters/min.)}}{\text{mean pulse rate/min.}}$$

$$\text{Stroke index (SI)} = \frac{\text{stroke volume}}{\text{body surface area}}$$

Total peripheral resistance (TRP) was estimated according to the formula

TPR

$$= \frac{\text{mean arterial blood pressure (mm.Hg)} \times 80}{\text{cardiac output (liters/min.)}}$$

$$\text{dynes/sec./cm.}^{-5}$$

and left ventricular work (LVW) or cardiac power was estimated according to the formula

LVW in kg. meters/min. = 0.0135
    × CO (l./min.) × MABP (mm. Hg).[8]

The following values were determined in duplicate in 75 patients before and following

TABLE 2. Recovery of Respiration After Anesthesia with Compound 347 (100 Patients)

	Radford Predicted Minute Volume (liters)	End of Anesth.		30 Minutes Post-Anesth.		60 Minutes Post-Anesth.	
		Rate/min.	M.V. (liters)	Rate/min.	M.V. (liters)	Rate/min.	M.V. (liters)
Mean	6.50	22	5.93	23	8.05	23	7.85
S.D.	1.15	5	3.74	6	3.71	5	2.82
S.E.M.	0.11	0.5	0.38	0.6	0.37	0.5	0.28

M.V. = minute volume; S.D. = standard deviation; S.E.M. = standard error of mean.

anesthesia: plasma histamine by the method of Noah and Brand [9]; serotonin by the method of Undenfriend, Weissbach and Brodie [10]; plasma catecholamines by the method of Anton and Sayre [11]; and plasma cortisol by the fluorescent method of Mattingly.[12] Serum sodium, potassium, chloride, inorganic phosphorus, transaminases (SGOT, SGPT), blood urea nitrogen, creatinine, glucose and carbon dioxide content were measured by standard laboratory procedures. Differential white blood cell counts and urinalyses were done preceding and following anesthesia.

The volume of anesthetic liquid used was recorded to determine the mean rate of utilization per minute.

All data were tabulated, transferred to IBM data cards and analyzed to determine the standard deviation and standard error of the means. In the comparative evaluation of methoxyflurane, anesthesia was conducted in the same manner except that methoxyflurane was administered through a Pentec vaporizer: the maximum concentration delivered was 1.5 per cent and the vaporizer was turned off when the abdominal fascia was being closed.

Results

CLINICAL OBSERVATIONS

The mean age of the patients, 44 men and 56 women, was 56 years, range 20 to 87 years. The median physical state of these patients was Class 3 (70 patients). Only two patients were in Class 1; there were 14 each in Class 2 and Class 4.

Following induction with gallamine and thiopental, a satisfactory depth of anesthesia was maintained easily with Compound 347 at a vapor concentration of 0.5 to 3.0 per cent, with 60 per cent nitrous oxide.

The pharynx and airway remained dry and the lungs were easy to inflate at all times. The skin was warm and dry and remained a good color. The pupils constricted after induction and remained fixed and small throughout. The conjunctiva usually became moderately injected.

Hiccup in three patients cleared spontaneously (in two) or after pharyngeal suctioning and deepening of anesthesia (in one). Excessive oozing or surgical bleeding did not occur. We did not observe muscle twitching or other signs of neuromuscular irritability. It was essential to administer Compound 347 *continuously;* otherwise anesthesia promptly lightened. Awakening and resumption of spontaneous respiration appeared within minutes after the anesthetic was discontinued. The orotracheal tube was usually well tolerated until the patient was awake and lucid. No patients were markedly restless or delirious during emergence.

Although respiratory reflexes were obtunded completely, the circulation remained sensitive to changes in the circulating blood volume and visceral traction. Blood pressure and pulse rate remained steady even after eight hours of anesthesia. Urinary drainage during most operations exceeded 50 ml. per hour, though only moderate volumes of intravenous solutions were administered.

Postanesthetic Pulmonary Ventilation and Recovery. At the end of anesthesia, pulmonary ventilation was restored promptly (table 2). During the 30 minutes immediately following anesthesia, 89 of the 100 patients were wide awake. The mean time to open the eyes on command was 11 ± 1 minutes; to show the tongue, 12 ± 2 minutes.

Twenty-seven patients developed nausea and/or vomiting during the first 24 hours. In

17, these symptoms were present in the first six hours; four patients had recurrent vomiting. More women (23 of 56) than men (4 of 44) had nausea and vomiting. In 15 of 27 patients, nausea and vomiting developed less than four hours after administration of a narcotic analgesic for the relief of pain. A nasogastric tube, used in 72/100 patients, reduced the incidence by approximately 50 per cent (16/72 vs. 11/28).

Postoperatively, circulatory signs remained stable in the absence of inadvertent surgical bleeding. Within 30 minutes after anesthesia, the blood pressure returned to preoperative levels (table 3). Shivering occurred in four patients even though there was a modest reduction in body temperature during the operation in almost every case. There were no complaints of after-taste or unpleasant breath odor during the day of recovery. The patients did not feel "groggy." Two patients had recurrent hiccup, one for two days and the other for three days, but this was not considered due to the anesthetic. Two patients had urinary incontinence, and three had to be catheterized on the first day after operation to relieve urinary retention.

Postanesthetic Pain. Awakening from anesthesia was accompanied by early pain and request for analgesic medication. During the first hour, 25 patients were given from 8 to 10 mg. alphaprodine (Nisentil®). By two hours after anesthesia, 59 patients had received narcotic analgesics and, by six hours, 62 patients were so medicated. Only 16/100 patients did not require medication in the first 24 hours.

Comparison with Methoxyflurane. The following observations were recorded from 100 patients (47 men and 53 women, mean age: 52 years). During the 30 minutes immediately following methoxyflurane anesthesia, 56 patients were awake. The mean time to open the eyes on command was 38 ± 5 minutes; to show the tongue, 47 ± 6 minutes. Twenty-eight patients developed nausea and/or vomiting during the 24 hours following the anesthetic. In 16 patients, these symptoms were present in the first six hours; seven patients had recurrent vomiting. Again, nausea and vomiting were more common among women than men (24 of 53 vs. 4 of 47); in ten of the 28 patients, the disturbance was related to medication for pain: nine of these were among those who had symptoms within six hours of anesthesia. In 66 patients, the use of a nasogastric tube similarly reduced the incidence of nausea and vomiting markedly (14 of 66 vs. 14 of 34). There was no statistical difference in the incidence of nausea and vomiting with Compound 347 and with methoxyflurane, but the early incidence of nausea and vomiting among the patients receiving Compound 347 appeared to be related to a greater need for medication for pain in this group.

Only two of 100 patients required medication for relief of pain during the first hour after methoxyflurane anesthesia. By two hours after anesthesia, 18 patients, and by six hours, 25 patients, were so medicated. An additional 28 patients were given narcotic analgesics for pain relief up to 24 hours after anesthesia with methoxyflurane. Patients who received Compound 347 obviously experienced pain much

TABLE 3. Changes in Blood Pressure (Auscultatory) and Pulse Rate (Palpatory) with Compound 347 Anesthesia*

	Before Induction			20 Minutes After			End of Anesthesia			30 Minutes Post-Anesth.			60 Minutes Post-Anesth.		
	S.B.P.	D.B.P.	P.R.	S.B.P.	D.B.P.	P.R.	S.B.P.	D.B.P.	P.R.	S.B.P.	D.B.P.	P.R.	S.B.P.	D.B.P.	P.R.
Mean	147	90	93	123	81	89	139	90	88	150	90	89	148	85	89
S.D.	26	14	14	21	15	10	21	14	12	32	16	13	30	16	14
S.E.M.	3	2	1	2	2	1	2	2	1	4	2	1	3	2	2

* No patient received a vasopressor at any time.
S.B.P. = systolic blood pressure; D.B.P. = diastolic blood pressure; P.R. = pulse rate.
S.D. = standard deviation; S.E.M. = standard error of mean.

earlier than those who received methoxyflurane.

Utilization of Compound 347 and Methoxyflurane. The amount of Compound 347 utilized in these 100 patients, with a mean duration of anesthesia of 170 minutes, was 0.5 ml. per minute. The amount of methoxyflurane utilized was slightly less than 0.25 ml. per minute. In both series, the median flow rate of nitrous oxide–oxygen was in the 8-to-10 liter per minute range. The cost of Compound 347 has not yet been determined.

Deaths. Four patients who received Compound 347 died, but anesthesia was judged not to be a major contributing cause.

One, a 61-year old man, had hypertensive heart disease and a Grade III harsh systolic murmur at the apex. During a right hemicolectomy for carcinoma, the electrocardiogram showed low voltage and occasional premature ventricular contractions. Operation and anesthesia were uneventful and the patient awoke promptly with stable vital signs. However, he complained of chest pain and dyspnea about two hours later; an electrocardiogram showed an anterior myocardial infarction. He was digitalized. Two days postoperatively, he developed recurrent bouts of hiccup which lasted two days and subsided spontaneously. On the sixth postoperative day, he developed slight jaundice which lasted four days. He made a gradual full recovery and was discharged in apparent good condition after 23 days in hospital. Three months later, he was readmitted with jaundice, in acute distress. He died a few days later. A large cerebellar tumor, found at postmortem examination accounted for his death.

The second patient, an emaciated 80-year-old woman, had inoperable carcinoma of the bowel with metastases. A colostomy was done. She recovered from the anesthetic promptly and appeared to be doing well for five days,

TABLE 4. Mean Effect of Anesthesia with Compound 347 on Blood Gases (100 patients)

		pH	Paco$_2$ mm.Hg	HCO$^-_3$ mM/L	Hct. %	Pao$_2$ mm.Hg	Sao$_2$ %
Control (day before)	Mean	7.448	38.5	26.0	40	72	97
	S.D.	0.036	5.2		5	11	2
	S.E.M.	0.004	0.6		0.6	1	0.2
Preanesthetic (after pre-medication)	Mean	7.445	36.6	24.2	40	75	97
	S.D.	0.038	4.1		5	20	2
	S.E.M.	0.004	0.5		0.6	2	0.3
During Anesthesia (mean of hourly samples*)	Mean	7.509	30.1	23.1	38	112	98
	S.D.	0.074	6.6		4	38	2
	S.E.M.	0.008	0.7		0.5	4	0.2
End of Anesthesia (on 100% oxygen)	Mean	7.362	43.8	23.5	39	251	99
	S.D.	0.051	7.4		4	99	1
	S.E.M.	0.006	0.8		0.5	11	0.1
30 Minutes after Anesthesia	Mean	7.382	42.3	23.9	39	80	96
	S.D.	0.039	5.6		4	26	3
	S.E.M.	0.004	0.6		0.5	3	0.3
60 Minutes after Anesthesia	Mean	7.392	41.3	23.8	39	80	96
	S.D.	0.048	6.3		4	30	3
	S.E.M.	0.005	0.7		0.5	3	0.3
24 Hours after Anesthesia	Mean	7.456	37.0	24.2	38	65	94
	S.D.	0.034	4.6		5	15	6
	S.E.M.	0.004	0.5		0.6	2	0.7

* Average of at least two samples.
S.D. = standard deviation; S.E.M. = standard error of mean.

then died abruptly. Postmortem examination was not permitted.

The third patient, a 63-year-old man, had uncontrollable diabetes mellitus. He was found to have inoperable carcinoma of the ampulla of Vater, hepatic cirrhosis and pancreatic fibrosis. A cholecystectomy was done and biopsies taken from the liver and pancreas. He recovered from anesthesia but bled. At reoperation six hours later, using nitrous oxide–oxygen–curare–endotracheal anesthesia, the abdomen was full of unclotted blood. Bleeding sites (including a torn cystic artery) were located and ligated. One hour and 20 minutes after the second operation began, blood pressure and pulse rate disappeared and he could not be resuscitated. At postmortem examination, marked coronary artery disease, duodenal ulcers and widespread lymph node metastases were found, in addition to a cirrhotic liver and carcinoma of the pancreas.

The fourth death occurred in a 71-year-old alcoholic, luetic, diabetic man who had obstructive jaundice, weight loss, abdominal pain and weakness. At operation, carcinoma of the head of the pancreas with metastases was found. A choledochoduodenostomy and liver biopsy were performed. The patient had an uneventful recovery from anesthesia. Six weeks after the operation, his condition deteriorated and he died.

LABORATORY OBSERVATIONS

Blood Gases (Table 4). Many patients were nervous when the initial blood samples were taken, as reflected by the high pH and lowered Pa_{CO_2}. Pa_{O_2}, on the other hand, was relatively low in spite of adequate saturation, reflecting the predominantly older patients. During anesthesia, moderate hyperventilation caused a slight respiratory alkalosis as evidenced by the changes in pH, Pa_{CO_2} and plasma bicarbonate. At the end of anesthesia, with the patient spontaneously breathing 100 per cent oxygen, pH and Pa_{CO_2} reflected shallow breathing, but the respiratory depression was not great and the patient recovered rapidly. No patients developed metabolic acidosis during or following anesthesia. The day after the procedure the only apparent change
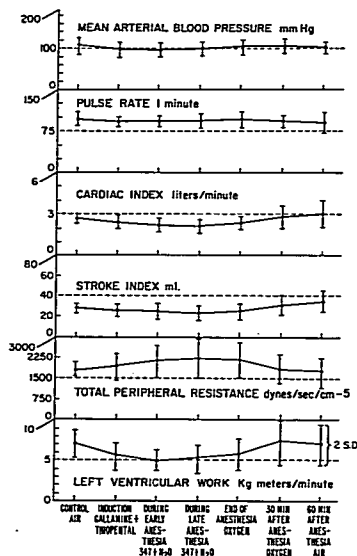

Fig. 1. Effect of anesthesia with compound 347 on circulatory dynamics in man.

in blood gases was a moderately decreased oxygen tension.

Circulatory Dynamics. The short-lived fall in blood pressure that occurs immediately after injection of thiopental for induction usually was followed by a gradual fall as Compound 347 was introduced. When surgical anesthesia was attained, blood pressure remained stable unless there was bleeding or visceral traction. At the end of anesthesia, blood pressure was only slightly below the control readings and was restored promptly upon recovery (table 3; fig. 1). Pulse remained steady throughout the anesthetic with a slight trend toward slowing, probably modified by the use of gallamine during induction. During recovery, blood pressure and pulse rate returned to the pre-induction values (table 3; fig. 1). No patients had significant alterations in the electrocardiogram.

Changes in the cardiac index were somewhat greater than might be inferred from the

blood pressure recordings. Induction with gallamine and thiopental lowered the cardiac index approximately 13 per cent, and addition of Compound 347 caused a further lowering of 9 per cent. The corresponding decreases in stroke index were 10 per cent and 20 per cent, respectively. Total peripheral resistance increased 7 per cent after induction and rose 24 per cent above control during administration of Compound 347. The work of the left ventricle fell 20 per cent during induction and a further 7 per cent during anesthesia. All alterations virtually disappeared within 30 minutes after anesthesia was discontinued (fig. 1). No changes in central venous pressure were observed.

Blood Elements and Blood Chemistry. Hemoglobin and hematocrit appeared to reflect changes incident to the surgical procedure. Although the calculated oxygen content was decreased, the measured oxygen saturation and tension were not decreased appreciably. There was a substantial rise in the white blood cell count, accompanied by a significant increase in polymorphonuclear leukocytes, in almost all patients (table 5).

Serum sodium and chloride were not altered appreciably, whereas serum potassium usually was reduced slightly. Carbon dioxide content tended to fall during anesthesia, but remained within the normal range. Blood urea nitrogen and creatinine, within normal limits in most patients, did not change significantly after anesthesia. Serum transaminases rose in most patients, but the elevation usually did not exceed the normal range (table 5).

Blood Sugar, Serum Inorganic Phosphorus, Plasma Cortisol and Biogenic Amines. Blood sugar rose approximately 50 per cent in all but a few patients, while serum inorganic phosphorus fell slightly. In all but one case, plasma cortisol rose to more than twice the control level. No significant alterations in histamine and serotonin occurred. Plasma epinephrine fell in a few more cases than it rose, whereas the plasma norepinephrine rose twice as often as it fell. Total catecholamines rose in most patients (table 5).

Discussion

In undertaking evaluation of this anesthetic, we decided to use it in procedures which would reveal immediately not only its anesthetic action, but its main drawbacks. Because we believe that all inhalation agents are respiratory depressants when administered at depths sufficient for major abdominal surgery, pulmonary ventilation was augmented in all cases until the abdomen was closed, and the rate of recovery of respiration was followed closely.

We reviewed in detail the question of whether to use nitrous oxide as a supplementary agent. Although 60 per cent nitrous oxide has virtually no effect on physiologic functions, it substantially reduces the vapor concentration required to produce satisfactory conditions [13] while allowing ample oxygen to be delivered. It not only reduces the hazards of a higher concentration of the vapor, but more often modifies undesirable than desirable responses as, for instance, it speeds induction and emergence from anesthesia and reduces the hypotensive effect of some agents by modifying the reduction in peripheral resistance.[14] Two practical considerations led us to the decision to add nitrous oxide: to decrease the amount of the anesthetic concentration for the sake of economy, and to compare our observations with previous similar studies with halogenated anesthetics in which we have used the same general technique along with nitrous oxide.[15-19]

INDUCTION AND EMERGENCE FROM ANESTHESIA

Because Compound 347 is less soluble in blood than halothane and much less soluble in blood than methoxyflurane, it is taken up very slowly from pulmonary alveoli, so that a rapid increase in alveolar tension brings a rapid rise in the brain tension and a rapid induction of anesthesia. When administration of vapor stops, there is a corresponding rapid emergence from anesthesia.

A pleasant odor makes the vapor well tolerated. It does not appear to stimulate excess salivation or tracheobronchial secretions or to affect bronchomotor tone.

Once surgical anesthesia is induced, tracheobronchial reactions to endotracheal tubes or suctioning are virtually absent. Controlled respiration is employed easily and no reaction is apparent when the lungs are hyperinflated.

TABLE 5A. Metabolic Changes Observed During Anesthesia with Compound 347

		Body Temp., Rectal ° C.	White Blood Cell Count ×1000	Polymorpho-nuclear Leukocytes %	Oxygen Content vol. %	Potassium mEq./L.	CO₂ Content mEq./L.
Before anesthesia	Mean	37.0	9.7	67	18.4	3.8	23.7
	S.E.M. ±	0.1	0.3	1	—	<.1	0.4
30 minutes after anesthesia	Mean	36.2	16.3	82	17.8	3.5	21.0
	S.E.M. ±	0.1	0.7	1	—	<.1	0.3

TABLE 5B. Metabolic Changes Observed During Anesthesia with Compound 347

		Blood Glucose mg./100 ml.	Serum Inorg. Phosphorus mEq./L.	SGOT Units	SGPT Units	Plasma Cortisol μg/100 ml.	Epinephrine μg./L.	Norepi-nephrine μg./L.
Before anesthesia	Mean	108	4.0	23.5	24.6	31.6	0.68	0.94
	S.E.M. ±	5	<0.1	1.7	2.5	1.3	0.15	0.12
30 minutes after anesthesia	Mean	161	3.2	38.3	33.7	69.9	0.49	1.27
	S.E.M. ±	7	<0.1	4.6	3.9	2.7	0.09	0.20

Muscular relaxation is good, as it is with methoxyflurane. During recovery, there is a rapid restoration of an adequate minute ventilation, exceeding that ordinarily seen after methoxyflurane anesthesia. Perhaps this indicates that Compound 347 has weak analgesic properties. If it has potent analgesic properties, they wear off very rapidly: many patients required narcotic medication for pain soon after recovery.

The incidence of nausea and vomiting following Compound 347 is similar to that seen after methoxyflurane for the same surgical procedures. The need for more analgesic medication after Compound 347 appeared to be an etiologic factor.

BLOOD GASES

Alterations in blood gases were almost the same as those which occur with other halogenated anesthetic procedures managed in the same way.[20–24] The only significant change was a slightly lowered oxygen tension the day after the anesthetic—almost always seen after major abdominal operations.[25–28]

CIRCULATION

Following induction of anesthesia with gallamine and thiopental, there is a slight fall in the blood pressure when Compound 347 is added, much the same as occurs with methoxyflurane and less than occurs with halothane.[15, 19] It is usually easy to check this effect by reducing the anesthetic concentration. The blood pressure appears to be the most useful sign of overdosage. Pulse rate tends to be somewhat higher than that seen with halothane and methoxyflurane, but is slightly lower than before induction of anesthesia. Pulse and ECG irregularities are conspicuously absent. Visceral traction reflexes are not as well depressed as respiratory tract reflexes, resulting occasionally in sharp hypotension which responds well to atropine and/or calcium chloride administration. At the end of anesthesia, blood pressure and pulse rate are usually within normal limits and remain stable during the rapid complete recovery of wakefulness and lucidity. There is remarkably little "hangover" later, and most patients have no retrograde amnesia for the period preceding induction of anesthesia.

The changes in cardiac performance, much the same as those which occur with methoxyflurane, are appreciably less than those seen with halothane, which has no effect on or may reduce peripheral resistance.[29]

In general, the circulatory effects of anesthesia with Compound 347 appeared rela-

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tively minor, suggesting a diethyl ether-like effect more than a fluorinated hydrocarbon effect.[30] It should be expected that sympatho-adrenal suppression will augment circulatory depression with this compound seriously.[31]

METABOLIC EFFECTS

Body Temperature. Body temperature probably was not affected significantly, although a consistent reduction in rectal temperature (slightly less than 1° C.), occurred over an average anesthesia time of approximately three hours. This is less than that observed with halothane anesthesia for similar procedures and much less than that which occurs with neuroleptanalgesia, but it is about the same as the reduction observed with methoxyflurane.

White Blood Cells. The leukocytosis and relative increase in polymorphonuclear cells that we observed in most patients following anesthesia with Compound 347 occurs following *all* potent anesthetics.[29, 32, 33, 34] Not necessarily a response to infection, this has been attributed primarily to the stress response which anesthetics initiate.

Hemoglobin, Hematocrit and Blood Oxygen. Administration of Compound 347 did not by itself affect the oxygen-carrying capacity or oxygen content of the blood. The relatively minor changes in oxygen saturation, oxygen tension, hemoglobin content and hematocrit were consistent with the anesthetic technique and the effects of the surgical procedure. Since cardiac output was depressed only moderately by this anesthetic, tissue oxygenation certainly was unaffected during and following operation.[4]

Blood Electrolytes and Carbon Dioxide Content. Serum sodium and chloride do not change during uncomplicated inhalation anesthesia, and no changes occurred in this study. On the other hand, the slight to moderate reduction in serum potassium that occurs with all inhalation and intravenous anesthetics occurred with Compound 347. The fall in serum potassium often is attributed to the effect of respiratory alkalosis,[35] but it occurs in the absence of respiratory disturbances and during mild hypercarbia.[36, 37] Numerous ex-

planations have been offered, but there is no consistent evidence to support any of them.[35–41]

The slight reduction in carbon dioxide content observed was within the normal variation that would be seen in the fasting state and after moderate hyperventilation.

Blood Urea Nitrogen, Creatinine and Transaminases. The absence of changes in blood urea nitrogen and creatinine and the slight rise in transaminases may indicate that Compound 347 has little or no effect on renal and hepatic function. Much greater use of this agent will be required to reveal whether hypersensitivity or toxic manifestations occur, since chemical changes in the blood occur only when parenchymal damage to these organs is extensive.

Plasma Cortisol, Blood Glucose, Serum Inorganic Phosphorus and Biogenic Amines. Plasma cortisol levels were increased twofold in almost all patients. This appears to be the normal adrenal cortical response to inhalation anesthetics and surgical stress.[42, 43, 44] The levels reached in these cases were of the order normally produced by ACTH stimulation.[12] No patients had initial levels that would indicate adrenal insufficiency or acute steroid suppression (<5 μg./100 ml.). Adrenocortical secretions are necessary not only for normal metabolic response, but also for satisfactory recovery after severe injury. As pointed out by Johnston, if adrenal function is impaired and cortisol is unavailable, circulatory homeostasis is threatened in a way which is not fully understood, and death from peripheral circulatory failure may result.[45] On the other hand, Vandam and Moore have suggested that anesthesia techniques which do not stimulate or even diminish cortical secretion may be of value when the metabolic response to trauma adds a considerable burden to the already-ill patient.[43]

Hyperglycemia also occurred consistently in the absence of glucose infusion in these cases, similar to that seen during diethyl ether and chloroform anesthesia, but not during anesthesia with fluroxene, trichloroethylene, halothane or methoxyflurane.[36, 37, 46, 47]

The blood glucose level rose to near 500 mg./100 ml. in a few patients to whom a 5 per cent dextrose in water infusion was ad-

ministered. This was higher than expected, indicating perhaps that this anesthetic, like ether, may cause intolerance to glucose.[45]

The slight fall of the serum inorganic phosphorus was not expected since, in previous studies, diethyl ether and cyclopropane caused a rise.[36, 37] We expect inorganic phosphorus to rise with blood sugar (although these two are not necessarily related) if the metabolic effects of the anesthetic are due predominantly to activation of the sympathoadrenal system,[48] as appears to be the case with Compound 347.

Assays of histamine and serotonin did not reveal significant changes, although the serotonin level tended to fall. Changes in plasma catecholamines were much larger but, because of the technical problems involved in their accurate estimation, it is necessary to be cautious in their interpretation.[49, 50] Norepinephrine levels rose twice as often as they remained the same or fell, consistent with the observed stability of the blood pressure and the elevated peripheral resistance. On the other hand, the epinephrine levels rose appreciably in only nine cases, fell in 15, and were virtually unchanged in the rest, which does not follow the consistent significant elevations of the blood sugar. However, there are no clear explanations for changes in blood epinephrine, sugar and inorganic phosphorus, with or without anesthetic agents.[36, 37, 43, 48]

Summary and Conclusions

An initial comprehensive clinical and laboratory evaluation of a new, potent, non-explosive, volatile, fluorinated ether anesthetic liquid with a pleasant odor, known as Compound 347 (2 chloro-1,1,2-trifluoroethyl difluoromethyl ether) was carried out during 100 major abdominal operations in patients. This anesthetic has no undesirable physical properties. It appears compatible with ancillary drugs.

Following induction of anesthesia with gallamine and thiopental, this compound was vaporized in a recalibrated Fluotec with 60 per cent nitrous oxide and 40 per cent oxygen, using a concentration of 0.5 to 3.0 per cent. It provided satisfactory hypnosis, analgesia and muscular relaxation in every case. The classical Guedel signs of diethyl ether anes-

thesia did not apply to this agent. Blood pressure depression was an appropriate sign of increasing depth.

Compound 347 produced a rapid anesthetic effect without gross disturbances of the airway, tracheobronchial tree, respiration, circulation or urine output. Recovery from anesthesia was rapid and smooth. During routine clinical anesthesia, vital signs were well maintained without vasopressors, bleeding was not excessive, and the electrocardiogram tracings were free of arrhythmias.

Blood sugar rose substantially during anesthesia, whereas serum inorganic phosphorus fell slightly. White blood cell counts rose. No appreciable alterations were observed in urinalysis, serum sodium and chloride, blood urea nitrogen, creatinine, transaminases, histamine or serotonin, while the serum potassium fell slightly. Adrenal cortical secretions were markedly elevated and there appeared to be an increase in plasma norepinephrine while plasma epinephrine tended to decrease.

Postanesthetic complications, such as nausea and vomiting, shivering, grogginess, unpleasant after-taste and hiccup were rare. No jaundice could be attributed to the use of this agent.

Compared with methoxyflurane, the awakening time with Compound 347 was much shorter, but medication for pain, required by more patients, probably augmented the incidence of nausea and vomiting. Approximately half as much methoxyflurane is required for a major anesthetic procedure.

We consider that Compound 347 deserves more extensive and comprehensive clinical evaluation to determine clearly whether it is indeed as safe, as free from side effects and as useful as it appeared in this study.

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Anesthesia

PLACENTAL TRANSMISSION   Many antibiotics of low molecular weight (440 or less) readily pass across the placenta. Colistimethate is a polypeptide (m.w. 1,200). Its concentration in maternal and fetal blood was studied, using antimicrobial effect on cultures of *Bordetella bronchiseptica* as an indication of blood concentration. A single intravenous dose to the mother resulted in a rapid rise in fetal blood level. Maternal and fetal blood levels remained elevated for more than eight hours. No drug could be detected in the amniotic fluid. The drug was also injected into amniotic fluid by transabdominal amniocentesis. Maternal and fetal blood levels rose slowly to barely detectable levels. No toxic effects were apparent in mother or fetus. This drug may be useful in treating or preventing intrauterine infection. (*McAulay, M. A., and Charles, D.: Placental Transmission of Cholistimethate, Clin. Pharmacol. Ther. 8: 578 (July) 1967.*)