The Effects of Cyclopropane Anesthesia without Surgical Operation on Mental Functions of Normal Man

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An investigation of mental function after profound and prolonged cyclopropane anesthesia without operation was conducted using as subjects 18 healthy men 21 to 24 years of age. Each subject was interviewed and tested prior to anesthesia and several times following anesthesia, for as long as a month later. Subjective and objective evidence of changes in mental performances were noted. Subjective impairment was often greater than objective measurements might indicate. Subjective complaints persisted for one to six days, with an average duration of three days. The greatest impairment detected by objective testing seemed to be in the ability to learn.

THE TIME REQUIRED to make a complete physical recovery following operation may be related to documented biochemical alterations which persist for as long as three to 12 months.[1] What is more difficult to explain is that during the past 25 years a number of patients have complained to various members of the Department of Anesthesia of not having regained preoperative mental abilities for periods as long as several months following an operation. Such decreases in ability to concentrate and mental acuity following surgical procedures prompted us to investigate the role of general anesthesia in producing postoperative difficulties in intellectual function.

It seemed important to separate the effects of the operation from those of the anesthetic so far as mental function was concerned. An opportunity to attempt this was offered by a study of normal human volunteers receiving prolonged and profound cyclopropane anesthesia without surgical intervention.

Methods

Studies of cerebral blood flow and metabolism in volunteer subjects from whom informed consent has been obtained have been conducted in this department for a number of years. The only significant interventions in this study were the placement of needles in the femoral artery and jugular bulb and the removal of 300 to 400 ml of blood, which was replaced with 1,500 to 2,000 ml of physiologic saline solution and 1,000 to 1,500 ml of 5 per cent glucose in water. Eighteen healthy white man, ranging from 21 to 24 years of age, were observed. Following an inhalational induction the subjects remained anesthetized with cyclopropane for three to six and a half hours. Inspired cyclopropane concentrations varied from 5 to 40 per cent, but each subject was exposed to a concentration of 20 per cent or more for at least 90 minutes. The trachea was intubated in all cases, and all subjects received *d*-tubocurarine intravenously to facilitate the control of respiration and toleration of the endotracheal tube when light anesthesia was employed. Neostigmine preceded by atropine was used in all cases to reverse the effects of *d*-tubocurarine. The arterial carbon dioxide tension was controlled during parts of the study. In 11 subjects it was constantly maintained close to 40 mm Hg; in seven it was maintained at three different levels, low (18 mm Hg), normal (40 mm Hg), and high (53 mm Hg), for approximately equal periods of time. Cyclopropane concentrations varied when P_{CO_2} was constant and cyclopropane remained constant when P_{CO_2} was varied.

Each of the 18 subjects was interviewed and

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tested prior to anesthesia and several times following anesthesia for as long as a month. They were asked about mood changes, sleep patterns and sleep disturbances, dreaming, irritability, their relationships with friends, as well as their powers of concentration and ability to think. While a printed form was not drawn up, a complete review of systems as used in history taking was followed in each case and every effort was made to minimize personal involvement of the interviewer.

During early trials of objective tests simple tasks such as memorization of serial digits and the ability to learn nonsense syllables proved to be unrevealing and were abandoned for more complex ones. Twelve subjects were given the two-part Nelson-Denny Standardization Reading Test for speed and comprehension. The two parts are equal in degree of difficulty. All 12 subjects took the first part a few days to a week before being anesthetized. Six were retested on the second post-study day and the other six five to seven days after anesthesia. Eight comparable men who had not been anesthetized served as controls for the reading tests. Eight subjects were examined with the Moran Repetitive Psychometric Tests designed to measure changes in mental performance over a period of time.[2] The Psychometric Measure Tests utilized in this study included those with the titles: Aiming, Number Facility, Visualization, Flexibility of Closure, Memory for Faces, and Perceptual Speed of Closure. They were administered a few days prior to the study and again on the first postanesthetic morning and the second postanesthetic afternoon. The control group for the Moran Tests consisted of 18 healthy, young male college or graduate students whose performances in these tests were the same as those of the study group prior to anesthesia (nonpaired Student's t tests $P > 0.2$ at a minimum for all tests).

Results

Subjective Changes

All individuals had subjective complaints during the first 24 hours after anesthesia (table 1). Seventy-eight per cent complained of weakness. An equal number were tired and listless. A few found watching television or reading the newspaper an extraordinary effort. Many found it difficult to concentrate on books or work which had been very interesting prior to the anesthetic experience. An illustration of decreased mental acuity was presented by one individual who had difficulty in operating a Xerox machine, a task which he normally found easy to perform. A number of subjects

Table 1. Subjective Changes in the First 24 Hours—18 Subjects

Per Cent of Subjects	Subjective Change
82	Decreased desire to smoke
78	Weakness
78	Tired, listless, decreased energy
72	Sore throat
67	Decreased ability to think and concentrate
61	Poor coordination
61	Dizziness, particularly when standing
50	Nauseated with motion
44	Abnormal thoughts or depression
39	Vomiting associated with motion
39	Poor appetite
33	Increased cough or sputum production
28	Nervous and restless
28	Sleep disturbances
28	Nausea without motion
22	Smelled odor of cyclopropane intermittently
22	Vomiting without motion
6	Tasted cyclopropane

Table 2. Subjective Changes Which Persisted for More Than 24 Hours—18 Subjects

Per Cent of Subjects	Subjective Change	Duration of Complaint in Days
67	Sore throat	3–4
64	Decreased desire to smoke	2–6
44	Tired, listless, decreased energy	2–6
28	Increased cough or sputum production	2–5
16	Smelled cyclopropane	2–14
16	Decreased ability to perform at job or school	3–6*
11	Poor coordination	2–3
11	Dizziness, particulary when standing	2–4

* One subject complained that it took a month for him to regain his preanesthetic ability to perform mental work; however, there is some doubt as to his reliability.

continued to have problems for several days after anesthesia (table 2). One to six days after the administration of anesthesia encompassed the range of time required for complete recovery in all but one subject. The third day after anesthesia was the average time at which subjects considered themselves to have returned to their prestudy states.

Although in our judgment all 18 subjects were exposed to prolonged and profound anesthesia, it was possible to identify five volunteers who had received the deepest anesthesia, *i.e.*, 36 to 40 per cent cyclopropane, end-tidal, for 90 to 135 minutes. These five had 90 to 135 minutes of 9.6 to 16 per cent cyclopropane, end-tidal, in addition. The six individuals with the least depths of anesthesia, 4.5 to 7 per cent, end-tidal, for 80 to 135 minutes, also breathed cyclopropane in 17 to 23 per cent end-tidal concentrations for 80 to 135 minutes. When the subjective complaints of the two groups were compared no differences were found. Subjective complaints of the 11 individuals maintained during anesthesias at normocarbia (35 to 41 mm Hg for three to four and a half hours) were no different from those reported by the seven subjects whose Pa_{CO_2} values reached highs of 53 mm Hg for two hours and lows of 19 mm Hg for similar periods.

Objective Tests

Results of two of the Moran Psychometric Measure Tests, Number Facility and Visualization, demonstrated noteworthy changes (table 3).

Number Facility tested the ability of the subject to perform simple addition problems. The score was based on the number of problems completed correctly in three minutes. The study subjects did not do as well as the controls on the second postanesthetic day. The controls improved their scores at a significant level of $P < 0.01$ (Student's t test). The study subjects failed to improve in the postanesthetic period.

A second test which showed some impairment was the Visualization Test (fig. 1). The subject was required to trace each line visually from its point of origin on the left to its termination on the right without the aid of a tracing finger or pencil. He was scored according to the correct number of answers in a three-minute period. The contrast between study and control groups was most marked on the first postanesthetic day. The difference in performance between study and control groups at this time was nearly equal to a significant t-test level of 0.05. On the second postanesthetic day the study subjects ($P > 0.1$) did

TABLE 3. Psychometric Measure Tests Which Demonstrated Impaired Mental Performance*

	Number Facility			Visualization		
	Day 1	Day 2	Improvement Day 1 to Day 2	Day 1	Day 2	Improvement Day 1 to Day 2
8 Experimental Subjects						
Mean	−2.00	−1.00	1.00	−2.38	2.25	4.62
S.E.	1.50	1.38	1.34	1.72	1.59	2.21
Significance of change (P values)	>1.0	>0.1	>0.1	>0.1	>0.1	>0.05
18 Control Subjects						
Mean	0.94	4.27	3.39	2.58	5.89	3.11
S.E.	0.85	1.32	1.36	1.56	2.78	1.58
Significance of change (P values)	>0.02	<0.01	<0.05	>0.1	<0.02	<0.2

* In these tests measurements were made of the performances by all of the subjects in the preanesthetic period and one and two days after anesthesia. The figures shown are changes in test scores (preanesthetic versus postanesthetic for postanesthetic days 1 and 2 and postanesthetic day 1 versus postanesthetic day 2). Statistical comparisons were done with the matched-pairs t test.

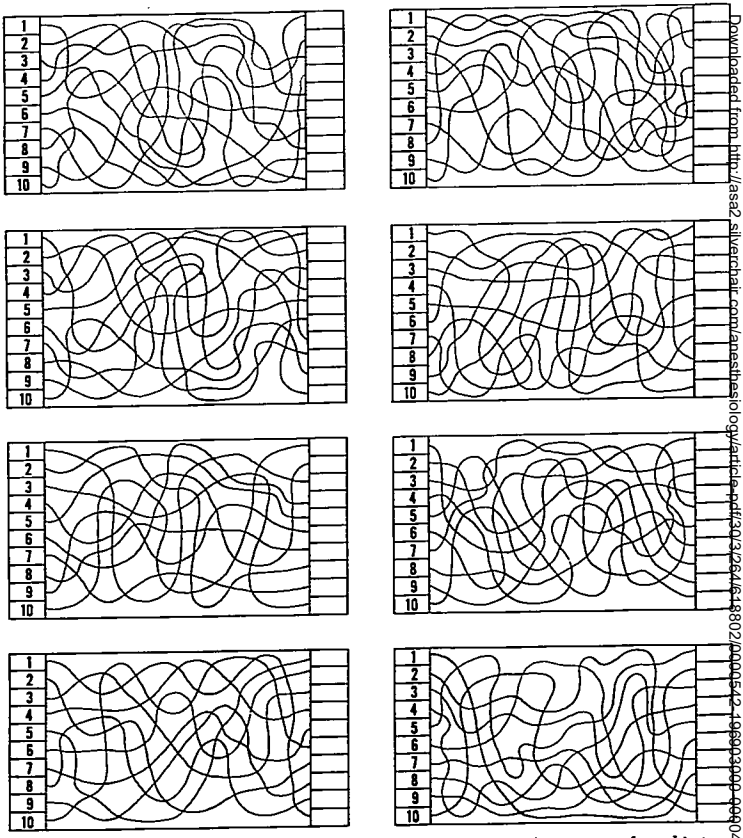

FIG. 1. Visualization Test. The ability of a subject to anticipate the outcome of an object manipulated in space is determined by this test. He must visually trace each line from its point of origin on the left to its termination on the right without the aid of a tracing finger. He is scored on the number of correct answers in a three-minute period.

not improve their scores significantly, while the controls ($P < 0.02$) did.

The average reading speed of 12 subjects after anesthesia, compared with their speed prior to anesthesia, decreased by 8.2 per cent. This contrasted with the eight control subjects, who demonstrated a 9.6 per cent gain in speed between the two tests. Due to the great variation in the scores of different individuals the changes after cyclopropane anesthesia were not statistically significant. However, 75 per cent of the controls improved the second time they were tested, as opposed to only 33 per cent of the experimental subjects ($P < 0.08$,

TABLE 4. Changes in Reading Speed and Comprehension in 12 Subjects*

	Speed in Words/Minute		Reading Comprehension	
	Experimental	Control	Experimental	Control
Mean	−42.33	20.62	3.66	6.00
S.E.	24.28	14.62	2.41	3.52
Significance of change (*P* values)	>0.1	>0.1	>0.1	>0.1

* In this test measurements of the performances of all subjects were made prior to anesthesia. In the postanesthetic period measurements were made on the second day in half the subjects and on the fifth to seventh day in the other half. Statistical comparisons were done by the *t* test method. The figures shown here denote changes in the test scores (preanesthetic versus postanesthetic).

chi square test). Reading comprehension improved 8 per cent in the study group and 17 per cent in the control group. Nine of the 12 experimental subjects showed improvements in reading comprehension, as compared with six of eight control subjects. The difference in comprehension was not statistically significant.

The results of the Psychometric Measures which failed to demonstrate impaired performance are illustrated in table 5. Both groups performed equally well in an Aiming Test which measures the ability to carry out quickly and precisely a series of movements requiring hand–eye coordination (fig. 2).

The Flexibility of Closure Test was also completed equally well or better in the postanesthetic period. This tests the ability to retain the image of a specified configuration despite the influence of other distracting configurations in the perceptual field (fig. 3).

Speed of Perception was also unimpaired. Here the subject is required to find a well-known symbol in a mass of material. The subject was presented with several rows of varying digits. To the left of each row a single digit was placed in a circle. The subject was to identify in each row those digits which were identical to the encircled digit to the left of that row.

Another test, Speed of Closure, failed to illustrate changes following anesthesia. In this test the subjects were required to unify an apparently disparate perceptual field into a single percept. The test consisted of rows of seemingly-disorganized letters. However, within these rows were several four-letter words, and the subject was graded on the number of these words which he was able to identify correctly.

A final test which failed to show statistically significant changes was the Memory for Faces

TABLE 5. Psychometric Measure Which Failed to Demonstrate Impaired Mental Performance in Eight Subjects*

	Aiming		Flexibility of Closure Perceptual Speed		Speed of Closure		Memory for Faces	
	Improved	Not Improved	Improved	Not Improved	Improved	Not Improved	Improved	Not Improved
Day 1								
Experimental	5	3	5	3	4	4	6	2	2	6
Control	5	3	6	2	4	4	8	0	5	3
Day 2								
Experimental	5	3	4	4	4	4	5	3	5	3
Control	4	3	4	3	4	3	6	1	7	0

* The figures in this table compare the numbers of subjects with and without inproved test scores. All subjects were tested in the preanesthetic period and during the first and second postanesthetic days. In all five tests the first and second postanesthetic day scores were compared with the preanesthetic scores. Differences in performance between the control and experimental group were not significant.

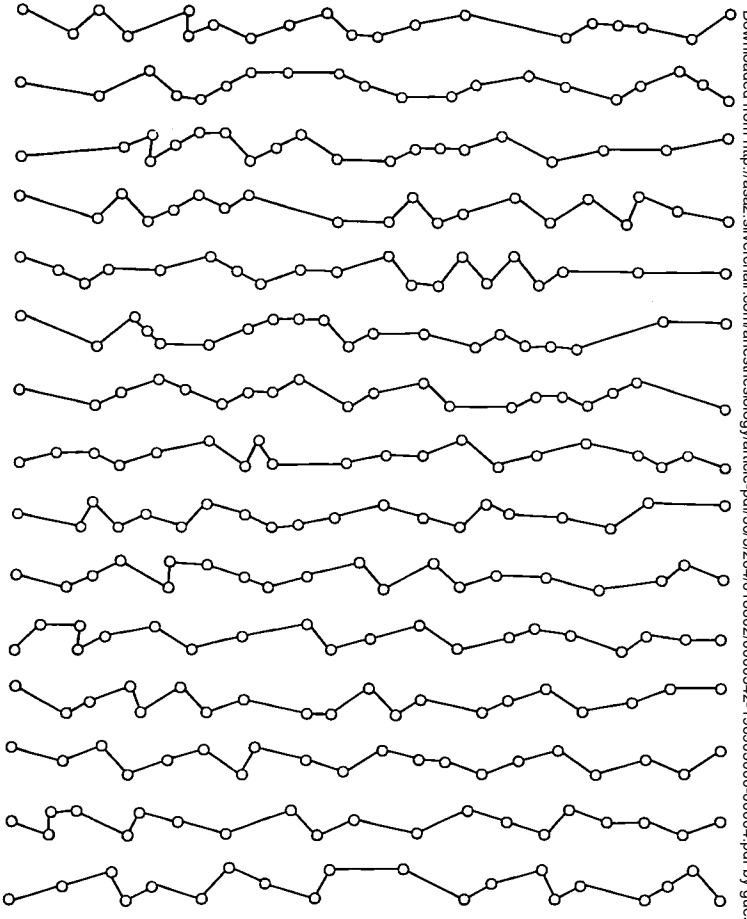

FIG. 2. Aiming Test. The aiming test requires eye–hand coordination. The subject must place a dot inside each of as many circles as possible in 90 seconds. The dot must not touch the edge of the circle. The score is based on the number of circles properly dotted.

Test. This test consists of a pair of sheets, each picturing groups of faces. The first sheet of the pair consists of 16 faces which the subject is given one minute to memorize. The second member of the pair contains 32 faces, 16 of which are the same as the initial 16

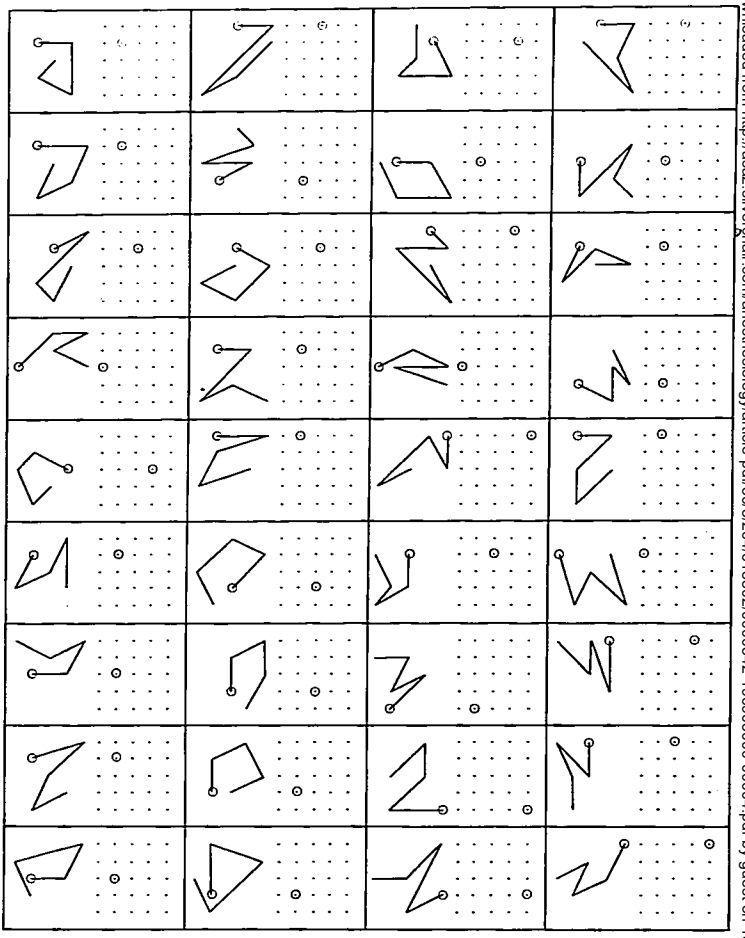

FIG. 3. Flexibility of Closure Test. This test requires the subject to retain the image of a specified configuration despite the influences of other distracting configurations in the perceptual field. There is a three-minute time limit. The subject must reproduce accurately as many of the figures as possible. He is permitted to use the dots in the right-hand portion of each box as guides.

faces. The subject must identify as many of these as he can in one minute. In completing this test the subject must demonstrate his ability to learn a critical item, retain it, and finally retrieve it from his memory. Valid statistical comparisons of the objective data obtained from subjects maintained at normocarbia and at altered levels of P_{CO_2} could not be made because of the small number of individuals involved.

Discussion

Mental function is obviously altered during and immediately after administration of general anesthetic agents. The duration, severity and practical significance of this effect have not, however, been studied, nor have attempts been made to separate these from the influence of the surgical procedure itself. Our data suggest that profound and prolonged but properly conducted cyclopropane anesthesia, *e.g.*, without hypoxia, is unlikely to cause reduced mental ability which lasts more than a week, at least in healthy young individuals. Although other inhalational anesthetic drugs will be studied, there is no *a priori* reason to believe that their actions will differ importantly from those of cyclopropane in this regard. Additional observations which are planned include those of different populations, such as older individuals and subjects with physical disabilities. This report, although preliminary, suggests that inhalational anesthesia may not contribute a great deal to prolonged postoperative reduction in mental acuity.

Could factors other than the pharmacologic actions of cyclopropane have influenced the results? Orne calls attention to the "demand characteristics of the experimental situation."[4] A subject trying to ascertain the true purpose of a study will respond in a way which supports the hypothesis under examination. Most people believe that there will be "after-effects" from general anesthesia. Being anesthetized was a dramatic event to the subjects in this study. They may have reacted to the event psychologically as well as showing effects of the anesthetic agent. It is difficult to separate the two, but clinically this is not important. We sought to determine the overall change in a subject's mental function.

A second nonanesthetic factor possibly affecting mental function is the personality of volunteers, which may differ from those of the population as a whole.[5, 6]

Finally, although we can find no data about the mental changes accompanying the loss of 300 to 400 ml of blood, it seems unlikely that there would be more than minimal effects in young healthy men, particularly after 12 hours or so. We believe, therefore, that the changes noted were due to the anesthetic.

An important difference between control and postanesthesia subjects seemed to be in the ability to learn. In the Visualization and Number Facility Tests control subjects improved at statistically significant levels on the second test day. The same degree of improvement did not occur in the post-cyclopropane group on the second postanesthetic day. The impairment of the ability to learn may prove to be a sensitive means of detecting objective changes in mental function in the postanesthetic period.

It is interesting to compare the findings in this study with those noted after acute sleep deprivation. When sleep-deprived subjects were challenged with self-paced adding tests, the speed of performance, but not accuracy, decreased.[3] In the Nelson-Denny Reading Test administered by us, subjects demonstrated decreases in reading speed in the postanesthetic period, but comprehension was not diminished. Williams *et al.* observed that the detrimental effects of acute sleep loss were greater for mental tasks of longer duration and greater monotony.[3] Our impression, based on interviewing, was that the ability to sustain mental effort was reduced in the postanesthetic period. Several volunteers returned to classes on the first postanesthetic day but were unable to complete the full schedule because of fatigue and loss of interest. Since the tests administered in this study required only 30 to 45 minutes for completion, we were in essence measuring the ability to perform mental tasks over short periods of time. However, two of the tests that demonstrated the poorest post-

anesthetic performances were at the end of the series of tests and required three to eight minutes to complete, as opposed to 90 seconds to two and a half minutes for the other tests.

Conclusions

Impairment of mental function after prolonged and profound cyclopropane anesthesia can be demonstrated, but it is brief, *i.e.*, of less than a week's duration. Subjective complaints apparently due to cyclopropane anesthesia without operation persisted for one to six days, with an average duration of three days. Results of two objective tests illustrate statistically significant changes in mental performance in the postanesthetic period. These were two of Moran's Psychometric Measure Tests: Number Facility and Visualization. Results of the Nelson-Denny Test for reading speed suggested a postanesthetic reduction in reading speed. Other psychological tests did not prove useful in identifying objective evidence of mental impairment in the first few postanesthetic days.

The author has the permission of Professor Moran to reproduce his tests.

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Drugs

CNS DEPRESSANTS Single therapeutic doses of pentobarbital, meprobamate, and tybamate were given to normal volunteers. There was relatively poor correlation between blood levels of the drugs and clinical symptoms measured simultaneously. This may be related to the difficulty of measuring effects in normal men who are influenced by social and personal factors more strongly than by small doses of central nervous system depressants. (*Hollister, L. E., and Clyde, D. J.: Blood Levels of Pentobarbital Sodium, Meprobamate, and Tybamate in Relation to Clinical Effects, Clin. Pharmacol. Therap. 9: 204 (March) 1968.*)

NONNARCOTIC ANALGESIC Methotrimeprazine (Levoprome) is an effective nonnarcotic analgesic administered only by intramuscular injection. This drug is about half as potent as morphine on a milligram basis and appears to cause less respiratory depression. However, because it may produce profound orthostatic hypotension and marked sedation, the use of methotrimeprazine is limited to nonambulatory patients. The use of a vasopressor such as levarterenol bitartrate may be indicated to counteract the hypotensive effect. Epinephrine should never be used in this situation because methotrimeprazine may reverse its action and produce profound hypotension. (*A.M.A. Council on Drugs: A Nonnarcotic Analgesic Agent, Methotrimeprazine (Levoprome), J.A.M.A. 204: 161 (April) 1968.*)