

Time Course of Mental and Psychomotor Effects of 30 Per Cent Nitrous Oxide during Inhalation and Recovery

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Two experiments were conducted testing the duration of action of nitrous oxide on human performance. In the first experiment, 11 subjects inhaled 30 per cent nitrous oxide for two periods of 40 min each, 45 min apart. Their mental and psychomotor skills were measured using free recall, tapping board, arithmetic and flicker fusion tests before and 2, 12, 22 and 32 min after establishing an end-tidal concentration of N₂O of 30 per cent. Recovery was tested using the same tests 2, 12, 22 and 32 min after discontinuation of N₂O. Eleven additional subjects inhaled oxygen only and served as a control group. In the second experiment, 8 subjects received both 30 per cent N₂O and oxygen in cross-over fashion, and their flicker fusion threshold was measured. When compared to baseline or oxygen administration, N₂O significantly impaired tapping rate, number of words recalled, and performance in arithmetic tests. The effects of N₂O were maximal at 2 min and remained similar throughout the entire administration. In flicker fusion tests, the effects of N₂O were similar to those of stimulant drugs; N₂O improved the subjects' ability to discriminate the fusion of flickering light. Recovery was complete in 22 min. The effects of, and recovery from the second administration of N₂O were similar to those of the first experiment. There was no evidence of development of tolerance to mental and psychomotor effects of the drug. (Key words: Anesthetic gases: nitrous oxide. Analgesia. Pharmacokinetics. Anesthetic potency:tolerance. Recovery.)

NITROUS OXIDE is commonly used to supplement other inhalational or intravenous anesthetic agents and for anesthesia or analgesia in obstetric, dental, and outpatient settings.^{1,2} It is also occasionally abused.^{3,4} Recently, the drug has been advocated as a tool for studying human memory.⁵

Although the kinetics of uptake and elimination of nitrous oxide have been adequately studied,⁶ the relationship between the kinetics of the drug and the course of the pharmacological effects produced have not been reported. Pharmacokinetics alone cannot directly determine the onset and the duration of

impaired mental and psychomotor functions during and after administration of nitrous oxide. Recently, Smith *et al.*⁷ reported that mice developed tolerance to the drug during the first 10 min of exposure. They postulated that if this phenomenon occurred in humans, it may have important clinical implications for the use of the drug in obstetric, dental, and outpatient practices.

The present study was designed to elucidate the time course of the effects of nitrous oxide on selected cognitive and psychomotor tasks. We measured performance on a tapping board, mathematical problems, free recall and flicker fusion threshold during a baseline period, and at selected intervals during two administrations of the drug and subsequent recovery periods. A second experiment involved further analysis of the flicker fusion test used in the main experiment.

Methods

SUBJECTS

Twenty-two healthy college students participated in the first experiment. Their mean age (\pm SD) was 23 \pm 2.3 years and their mean weight (\pm SD) was 64.5 \pm 9.7 kg. Eleven of the subjects were males and eleven were females. None of them were taking any medications. The nature and purpose of the study were explained to the subjects, and they signed an appropriate consent form. The study protocol was approved by the University of Iowa Committee on Research Involving Human Subjects.

PROCEDURE

The subjects were instructed to abstain from any stimulant or depressant beverages from 5:00 P.M. on the day preceding the study and to sleep a minimum of 8 hours during the night. The scheme of experimental procedures is summarized in table 1. Upon arrival at the laboratory, the subjects practiced four times on each test in a manner similar to that used during the actual test in order to become accustomed to the mouthpiece, nose clip, dry gases, etc. Fifteen min after the practice session, they were tested again with the mouthpiece and noseclip in place, to obtain baseline control results while breathing 100 per cent oxygen.

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Subjects began the actual test 5 min after the pre-treatment results were obtained, by inhaling either 30 per cent nitrous oxide in oxygen (five males and six females) or 100 per cent oxygen (five males and six females) in random order. For subjects receiving nitrous oxide, the end-tidal concentration was continuously monitored using an infrared analyzer (Beckman LB-II®). It took an average of 5 min until the 30 per cent end-tidal concentration of nitrous oxide was reached. Thereafter, this concentration was continuously maintained throughout the inhalation period.

The battery of objective tests; (tapping board, free recall, mathematical problems, and flicker fusion) was repeated at 2, 12, 22 and 32 min after reaching the 30 per cent end-tidal concentration of nitrous oxide. The subjective questionnaire was answered after the 32-min tests. This part of the study is termed the first drug administration period. The subjects then started to breathe room air and the tests were repeated at 2, 12, 22 and 32 min following the cessation of administration of the nitrous oxide or oxygen. This part of the study is termed the first recovery period.

Following the recovery period, the subjects were given a 15-min rest period followed by another 45 min of inhalation of the same gas that they had received during the first session. The objective tests were repeated at 12 and 32 min after reaching the 30 per cent concentration of nitrous oxide. After this second gas administration, the subjects breathed room air and 32 min later the critical flicker fusion and free recall tests were performed. The subjective questionnaire was repeated both at the end of the second gas administration and at the end of the second recovery period.

TESTS

The following five tasks were performed and evaluated.

Tapping Board. The subjects were asked to tap metal target areas at alternate ends of a 55-cm board with a metal stylus as rapidly as possible.⁸ Three 10-s tests were administered. A 10-s rest period followed each trial. The score was recorded as the total number of taps made during the three trials.

Free Recall. Subjects listened to a list of twelve words presented by a tape recorder at the rate of one word/2 s.⁹ Immediately after presentation, the subjects were asked to write in any order, as many words as they could remember over a period of 1.5 min. A different list was used at each time period. The words were all

TABLE 1. Scheme of Experimental Procedures

Approximate Time	Procedure
8:00 am or 1:00 pm	Practice session: objective tests.
8:30 am or 1:30 pm	Baseline results: objective tests and questionnaire.
8:40 am or 1:40 pm	5-min intermission.
8:45 am or 1:45 pm	First administration: inhalation of O ₂ or N ₂ O starts.
8:50 am- or 1:50 pm- 9:30 am 2:30 pm	Objective tests: repeated at 2, 12, 22 and 32 min; subjective questionnaire done at 32 min.
9:30 am or 2:30 pm	First recovery: inhalation of room air starts.
9:30 am- or 2:30 pm- 10:10 am 3:10 pm	Objective tests: repeated at 2, 12, 22 and 32 min; subjective questionnaire done at 32 min.
10:10 am or 3:10 pm	Rest period.
10:25 am or 3:25 pm	Second administration: inhalation of the same gas starts again.
10:40 am- or 3:40 pm- 11:20 am 4:20 pm	Objective tests: repeated at 12 and 32 min; subjective questionnaire done at 32 min.
11:20 am or 4:20 pm	Second recovery: inhalation of room air starts again.
11:57 am or 4:57 pm	Free recall test and subjective questionnaire repeated.

nouns and had a frequency of 10–40/million according to the Thorndike-Lorge word count.¹⁰

Mathematical Problems. The subjects were asked to solve as many two-digit addition problems as possible within 1.5 min. The total number of problems attempted and the number correct were scored.

Critical Flicker Fusion. The subjects' flicker fusion response threshold was measured with a Lafayette Model No. 12020® using a viewing chamber No. 12024® (Lafayette Instrument Co., Indiana). The subjects looked at a flickering light as the experimenter slowly increased the rate of flickering and were asked to raise their hand when it looked continuous. The frequency was always gradually increased by increments of 1 Hz every second starting from 24 Hz.

Subjective Assessments. The subjects rated their feelings on eight visual analogue scales.⁸ The eight adjective pairs used fell into each of four categories of feelings: physical sedation, mental sedation, tranquilization, and motivation. At the end of the second inhalation period, subjects were asked which gas administered at each session had been more potent or whether the effects had been similar. They were also asked whether they thought they had received oxygen or nitrous oxide.

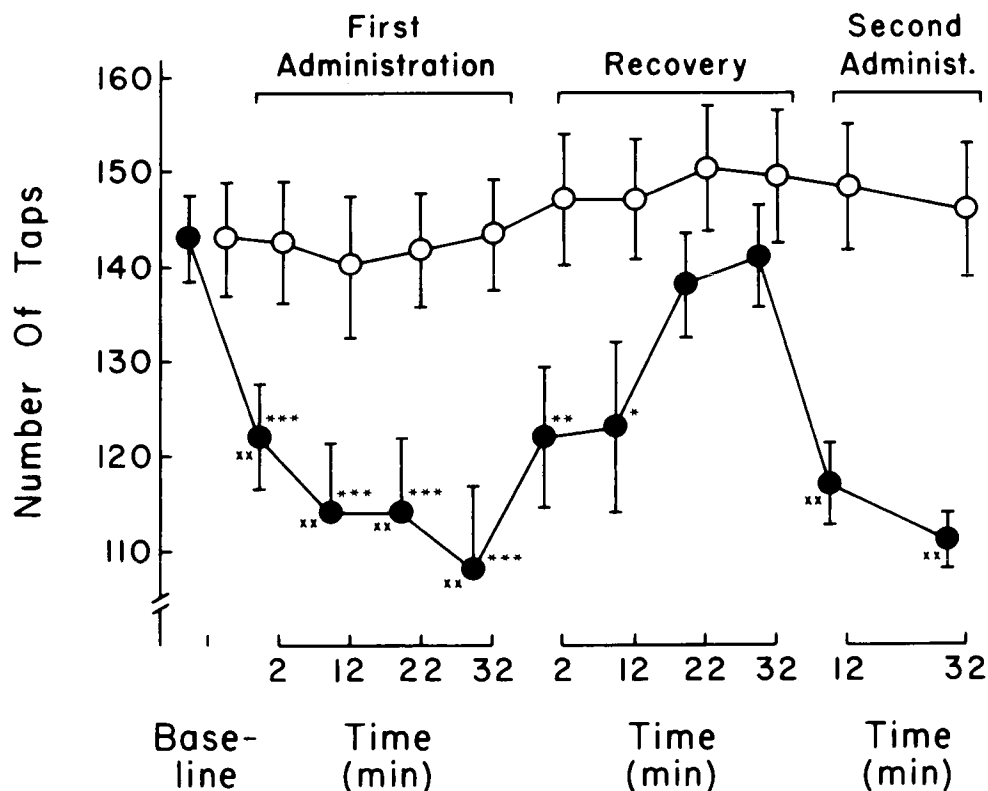


FIG. 1. The mean number of taps (\pm SE) in the tapping board test before, during and after repeated administration of 30 per cent nitrous oxide (●) or oxygen (○). The abscissa represents the time after reaching 30 per cent end-tidal concentration of nitrous oxide during its inhalation and time after discontinuation of the gas during recovery phase. * $P < 0.01$; ** $P < 0.005$; *** $P < 0.001$ vs. baseline and ** $P < 0.005$ vs. oxygen.

STATISTICS

A multivariate analysis of variance was used for statistical treatment of the results. Multiple comparisons were used to look at pairwise differences. The level of significance for each test was $P < 0.05$.

Results

The peak effects of nitrous oxide on mental and psychomotor performance were reached 2 min after achieving the 30 per cent end-tidal concentration and the effects remained similar throughout the inhalation. The effects of the second administration did not differ from those of the first administration. There was no evidence of development of tolerance to the drug.

Tapping Board. (fig. 1) As is apparent in the figure, nitrous oxide significantly impaired performance compared to the oxygen or baseline scores, which did not differ significantly from each other [drug effect, $F(1,17) = 15.0$, $P = 0.002$; time effect, $F(4,15) = 7.62$, $P = 0.002$]. The performance was impaired at the 2-min testing period and remained impaired throughout the remainder of the nitrous oxide inhalation. Within the nitrous oxide group, the results at 2, 12, 22 and 32 min did not differ significantly from each other. Twelve min after discontinuation

Because of failure of the flicker fusion test to reveal the effects of nitrous oxide in the first experiment, we decided to analyze the effects of the drug on flicker fusion threshold in a more detailed way.

Eight subjects (four males and four females) of approximately the same age and weight as those in the first experiment inhaled both nitrous oxide-oxygen and oxygen administered as before. On the first administration, four of the subjects received nitrous oxide and the other four received oxygen, whereas on the second administration, the gases were reversed. The subjects' flicker fusion frequency response threshold was measured before and after 37 min of inhalation of nitrous oxide-oxygen (32 min at 30 per cent end-tidal concentration) and oxygen alone.

Both the flicker threshold and the fusion threshold were measured at high light intensity (the maximum for the apparatus) and at low light intensity (half the maximum for the apparatus). Four recordings were made at each setting and the mean was used as the result. The flicker threshold was assessed as in the first trial by asking the subjects to raise their hand when they thought the light had stopped flickering. The fusion threshold was assessed by asking the subjects to tell when a continuous light started flickering while decreasing the flicker frequency. The frequency was always gradually increased or decreased by an increment of 1 Hz/s.

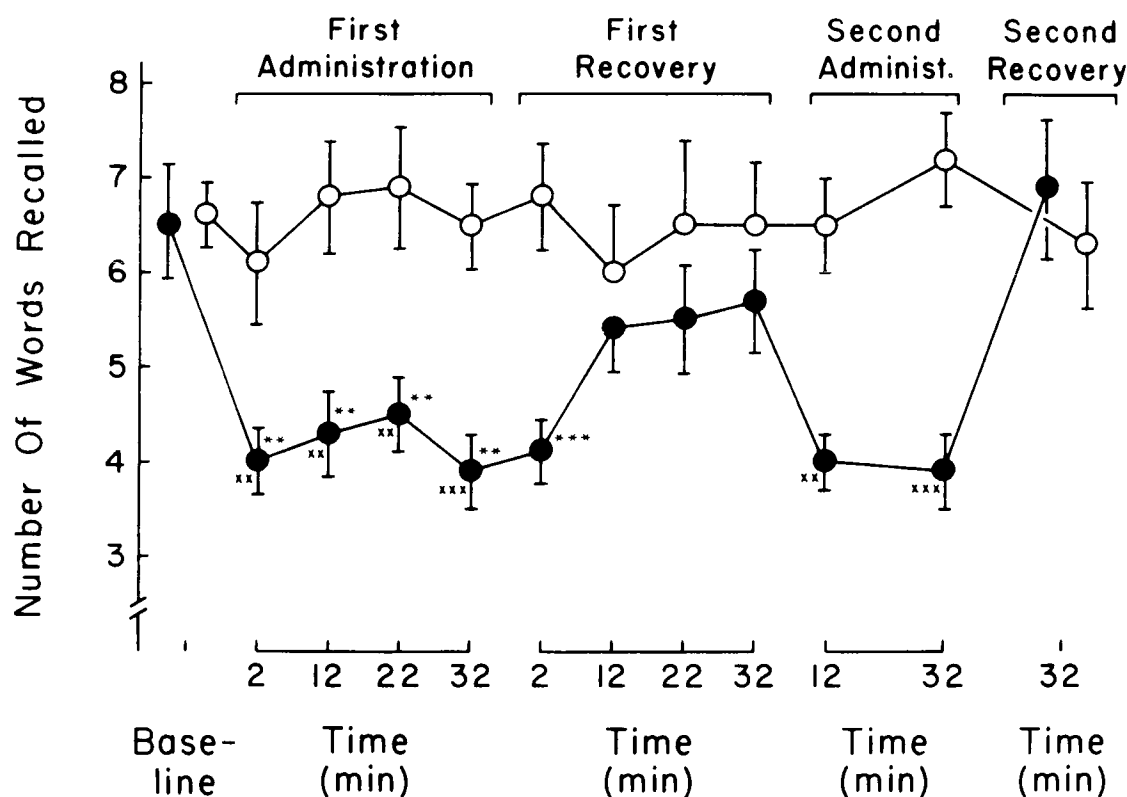


FIG. 2. The mean number of words recalled (\pm SE) in the free recall test before, during and after repeated administration of 30 per cent nitrous oxide (●) or oxygen (○). The abscissa represents time after reaching 30 per cent end-tidal concentration of nitrous oxide during its inhalation and time after discontinuation of the gas during recovery phase. ** $P < 0.005$; *** $P < 0.001$ vs. baseline; ** $P < 0.005$; and *** $P < 0.001$ vs. oxygen.

of the nitrous oxide, the number of taps recorded was still significantly lower than that before the administration of the gas, but at 22 min the performance had returned to baseline (fig. 1). The effects of the second administration of nitrous oxide were similar to those measured during the first administration [$F(1,18) = 0.21$, $P = 0.66$].

Free Recall. (fig. 2) Oxygen did not modify the subjects' ability to remember the words in the free recall test. When compared to the baseline or oxygen administration, nitrous oxide significantly decreased the number of words recalled [time effect, $F(4,15) = 4.82$, $P < 0.01$; drug effect, $F(1,17) = 23.6$, $P < 0.001$]. The effect was present at the 2 min testing period and remained unaltered throughout the rest of the inhalation period. Recovery of free recall performance was more rapid than that of the tapping rate. Performance returned to baseline by 12 min after discontinuation of the nitrous oxide. No differences were found between the effects of the first and second administration of nitrous oxide [$F(1,18) = 0.22$, $P = 0.646$], and recovery was similar after both administrations.

Mathematical Problems. (fig. 3) As with the tests already described, oxygen administration did not alter the results of the mathematical tests, but nitrous oxide impaired both the speed and accuracy of the subjects. When compared to the baseline and oxygen administration, nitrous oxide significantly decreased both the number of problems attempted, and the number of problems answered correctly with the impairment being approximately equivalent during each observation [time effect, $F(4,15) = 15.6$, $P < 0.001$; drug effect, $F(1,17) = 46.4$, $P < 0.001$]. Recovery was complete by 2 min after discontinuation of nitrous oxide. The effects of the second gas administration were similar to those of the first administration [$F(1,18) = 3.10$, $P = 0.092$].

Critical Flicker Fusion. The subjects' flicker threshold did not change from the baseline after either oxygen or nitrous oxide administration [drug effect, $F(1,17) = 0.01$, $P = 0.982$].

Subjective Assessments. Subjective assessments are listed in table 2 and show that nitrous oxide induced significant ($P < 0.005$) mental and physical sedation as well as relaxation when compared to the baseline or

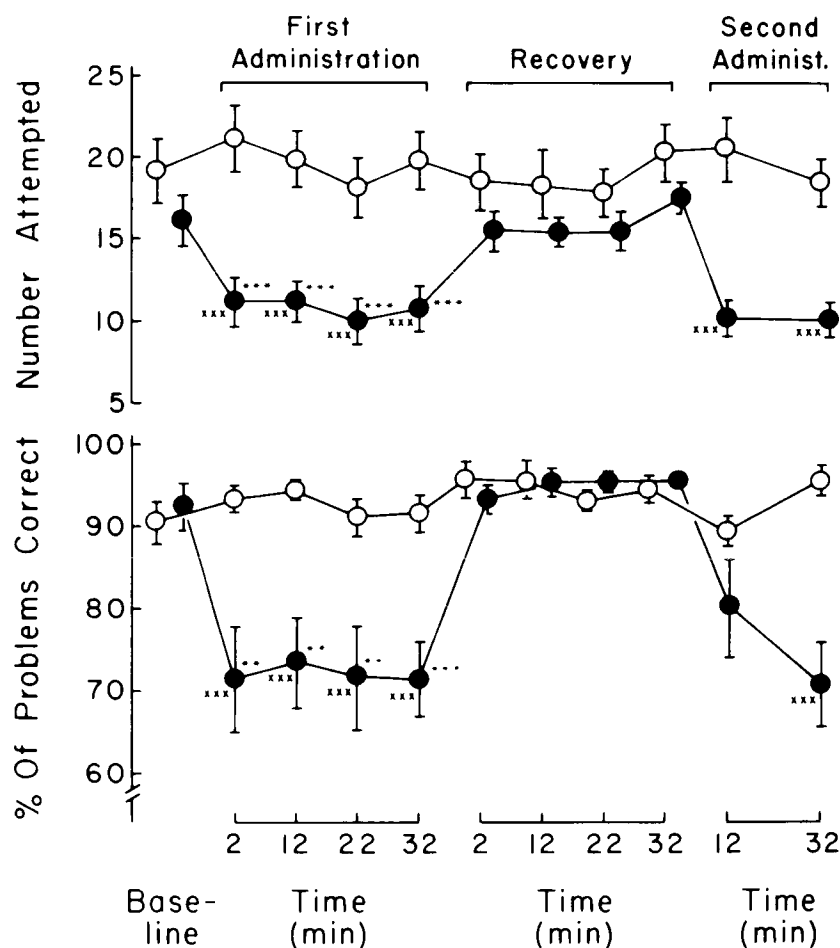


FIG. 3. The mean number of problems attempted and the percentage of problems correct (\pm SE) in the mathematical test before, during and after repeated administration of 30 per cent nitrous oxide (●) or oxygen (○). The abscissa represents time after reaching 30 per cent end-tidal concentration of nitrous oxide during its inhalation and time after discontinuation of the gas during recovery phase. ** $P < 0.005$; *** $P < 0.001$ vs. baseline; and *** $P < 0.001$ vs. oxygen.

oxygen administration. The subjective assessments were similar after the first and second administrations. The subjects' motivation did not change after either oxygen or nitrous oxide administration. Six of the eleven subjects who received oxygen thought they had received nitrous oxide when asked at the end of the

experiment, while eight of the eleven subjects who actually received nitrous oxide thought they had received nitrous oxide.

The results in the second experiment are listed in table 3 and show that the flicker threshold, *i.e.*, increasing the frequency of flickering, was sensitive to

TABLE 2. Subjective Assessments on Visual Analogue Scales Before, During and After Repeated Administration of 30 Per Cent Nitrous Oxide or Oxygen (Means \pm SD of 11 Subjects)

Parameter Measured	Treatment	Baseline	Time of Assessment			
			At the End of First Administration	After First Recovery	At the End of Second Administration	After Second Recovery Period
Physical Sedation (0 = nil; 100 = severe)	Oxygen N ₂ O	38 \pm 10 41 \pm 18	45 \pm 12 66 \pm 21†‡	43 \pm 19 51 \pm 21	52 \pm 13 63 \pm 27**	49 \pm 22 36 \pm 20
Mental Sedation (0 = nil; 100 = severe)	Oxygen N ₂ O	37 \pm 17 38 \pm 15	52 \pm 16* 74 \pm 18†‡	44 \pm 23 40 \pm 19	50 \pm 17 78 \pm 17†‡	46 \pm 27 27 \pm 12
Tense-relaxed (0 = relaxed; 100 = tense)	Oxygen N ₂ O	46 \pm 26 37 \pm 13	41 \pm 16 17 \pm 19*	33 \pm 20 40 \pm 10	51 \pm 20 15 \pm 14*‡	37 \pm 26 19 \pm 10
Motivated-unmotivated (0 = motivated; 100 = unmotivated)	Oxygen N ₂ O	48 \pm 21 36 \pm 22	58 \pm 16 50 \pm 30	58 \pm 22 55 \pm 27	60 \pm 20 59 \pm 34	54 \pm 28 39 \pm 23

* $P < 0.05$; † $P < 0.001$ vs. baseline; ‡ $P < 0.005$ vs. oxygen.

the effects of nitrous oxide but not for the fusion threshold, *i.e.*, decreasing the frequency of flickering. When the flicker threshold was tested, the subjects were able to discriminate the flickering light significantly ($P < 0.05$) better under nitrous oxide than under oxygen inhalation. The test was more sensitive when the high intensity light was used than with the low intensity light.

Discussion

The present study was designed to assess the time course of mental and psychomotor effects of 30 per cent nitrous oxide. Because of its wide use in outpatient anesthesia and for pain relief, as well as its potential use in studying memory functions and effects of inert gas narcosis, it is important to know when the maximum effect of the gas is reached and how long it takes for full mental and psychomotor recovery. We also wanted to find out whether acute tolerance to the mental effects of nitrous oxide develop in humans.

In the first experiment, a double-blind design was maintained because six of eleven subjects receiving oxygen thought they received nitrous oxide whereas three of eleven subjects given nitrous oxide thought they received oxygen.

The tapping board was used to assess psychomotor performance involving eye-hand coordination. Impairment was rapid, remained constant and persisted the longest of any of the tasks after the drug was discontinued. Eye-hand coordination has been shown previously to be diminished by 25 per cent nitrous oxide administrations,¹¹ and judging from the present results, this is a very sensitive measure of the residual effects of the drug. This is a simple test to administer and could be used as a quick index of a patient's capacity to resume normal activities, *e.g.*, discharge from hospital, following nitrous oxide administration.

Free recall procedures are the most popular techniques reported in contemporary memory literature.¹² They are sensitive and reliable measures of memory components and are similar to daily memory demands.¹² Several studies have indicated the sensitivity of free recall in detecting effects of nitrous oxide on the central nervous system.¹³⁻¹⁵ The present results indicated that free recall was impaired early in the administration (2 min) but recovered fairly rapidly when the drug was withdrawn (12 min).

The arithmetic test was used because it is easy to administer and could also be easily used in clinical practice. The rapid return of the subjects' mathematical ability to baseline, however, suggests that the test is of little value when assessing the residual effects of nitrous oxide.

TABLE 3. The Ability of Eight Subjects to Discriminate Flickering Light. Means \pm SD of Baseline Values and Changes \pm SD from These Values Under 100 Per Cent Oxygen (Placebo) or 30 Per Cent Nitrous Oxide Inhalation

Parameter	Baseline (Hz)	Oxygen (Hz)	Nitrous Oxide (Hz)
High light intensity			
Flicker threshold	39.5 \pm 2.7	+0.6 \pm 1.4	+5.1 \pm 3.4*
Fusion threshold	42.4 \pm 3.4	-0.8 \pm 2.5	-3.2 \pm 4.0
Low light intensity			
Flicker threshold	35.7 \pm 2.7	+1.0 \pm 2.2	+5.3 \pm 2.7†
Fusion threshold	36.8 \pm 5.9	-1.6 \pm 8.1	-1.9 \pm 5.8

* $P < 0.005$ vs. oxygen; † $P < 0.01$.

Several drugs have been shown to impair performance on critical flicker fusion,¹⁶⁻¹⁹ while relatively few, *e.g.*, amphetamine and marijuana, have been shown to improve performance.¹⁹ Unexpectedly, nitrous oxide improved performance in this test. Recently Wernberg *et al.*²⁰ also found that nitrous oxide improved flicker fusion response threshold. Since most anesthetics and adjuvants tend to impair performance on this task, it is not clear why nitrous oxide aided the subjects, particularly when it decreased performance on all the other tasks. At any rate, this measure does not appear to be satisfactory for the assessment of residual behavioral effects of nitrous oxide if combined with other depressants.

Tolerance to the analgesic effect of nitrous oxide for the treatment of intractable pain has been observed.²¹ Whitwam *et al.*²² also found acute tolerance to the analgesia of nitrous oxide in some subjects during a 45-min exposure. However, Langley *et al.*,²³ using somatic-evoked brain responses during nitrogen narcosis, found only slight evidence of adaptation (nitrous oxide in 30 per cent concentration is equipotent to a depth of 70 m of sea water²⁴). A close correlation between the pharmacokinetic behavior of nitrous oxide,⁶ and the kinetics of its mental and psychomotor effects was observed in our study. Our results did not suggest development of tolerance to mental and psychomotor effects of nitrous oxide in humans, at least over the first 45 min of administration. However, unlike mental and psychomotor effects, the kinetics of analgesia produced by the gas apparently do not parallel the kinetics of its uptake and distribution,²² which may suggest an "indirect" relationship between the brain concentration of nitrous oxide and its analgesic effect.

The distinct impairment in hand-eye coordination 12 min after cessation of the administration of 30 per cent nitrous oxide, suggests that even in healthy young subjects, total recovery after its inhalation is

not instantaneous, and that outpatients need supervision for at least 20–30 min after administration.

In summary, a close correlation between the pharmacokinetics of nitrous oxide and the kinetics of its behavioral and psychomotor effects was observed. While reports of tolerance to the analgesic effects of nitrous oxide have been made, there was no evidence for change in behavioral effects during or between the two 45-min exposures.

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