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Psychological Effects of Halothane and Isoflurane Anesthesia

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Psychological effects of halothane (16 subjects) and isoflurane (24 subjects) anesthesia on healthy young men were assessed prior to and 2, 3, 4, 6, 8, and 30 days after anesthesia. The results with each agent were compared with each other and with the results for 41 unanesthetized controls. Both agents altered psychological function. Changes in function were greatest 2 days after anesthesia; function had returned to near preanesthesia values 8 days after anesthesia. Only slight symptom and mood effects and no intellectual effect attributable to anesthesia remained 30 days after anesthesia. Halothane produced greater negative effects on moods and symptoms and tended to produce greater negative effects on intellectual function than did isoflurane. The differences between the two anesthetics are consistent with differences in their solubilities and metabolism. (Key words: Anesthetics, volatile, halothane; Anesthetics, volatile, isoflurane; Psychologic function, postanesthetic.)

PSYCHOLOGICAL CHANGES that may follow anesthesia have received relatively little systematic study despite their potential importance. Some investigators have attempted to quantify behavior immediately after anesthesia,[1,2] while others have studied more prolonged postanesthetic effects.[3-5] Although these investigations have produced useful data, each possesses ambiguities as a result of failure to include one or more of the following factors: quantification and objectivity of behavioral measurement; comprehensiveness of behavioral measurement; adequate controls; isolation of anesthetic from surgical effects.

This study compared the behavioral effects of the most commonly used potent inhalation anesthetic, halothane, with those of isoflurane (Forane¶). The study was part of a comprehensive physiological comparison of effects of these two anesthetics on physiologically normal young men anesthetized without also undergoing surgical procedures.[6,7] Our hypotheses were that: 1) both anesthetics would produce short-term (to one week) reductions in adaptive functioning and increments in subjective symptoms; 2) the anesthetics would differ in their short-term, but not in their long-term, effects; 3) there would be no residual effect of anesthesia 30 days afterwards.

Methods

Eighty-one male volunteers willing to undergo anesthesia for pay were recruited by advertising on local college campuses. We included control groups to evaluate changes in anesthetized subjects relative to expected practice or repeated measurement effects. Because the halothane and isoflurane subjects were sampled at different points in time and differed in modal school affiliation, we separated the control subjects into those recruited with the halothane experimental subjects (halothane controls) and those recruited with the isoflurane experimental subjects (isoflurane controls). While none of the halothane controls was exposed to any anesthesia or to the environment in which anesthesia was administered, a subgroup of the isoflurane controls was exposed to a subanesthetic dose of isoflurane; this group, supplementary isoflu-

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TABLE 1. Age, Education, and Preanesthesia IQ's of Experimental and Control Groups

	N	Age (Years)		Education (Years)		Verbal IQ		Performance IQ		Full Scale IQ	
		$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Halothane, experimental	16	22.8	2.8	15.1	.9	126.8	8.9	116.3	10.2	123.7	8.9
Isoflurane, experimental	24	24.7	2.4	14.8	1.6	119.8	7.5	110.6	10.2	116.8	7.3
Halothane, control	16	25.7	2.5	15.2	1.0	124.2	6.2	116.6	8.9	122.2	7.2
Isoflurane, control 1*	16	25.4	3.6	15.4	1.2	120.2	10.4	111.0	6.8	117.2	8.2
Isoflurane control 2†	9	24.1	1.8	14.9	1.5	‡	‡	‡	‡	‡	‡
Significance of overall group differences		.05		NS		.05		NS		.05	

* Primary isoflurane controls.
† Supplementary isoflurane controls.
‡ IQ measures were not obtained for supplementary isoflurane controls.

rane controls, constituted a third control group. Subjects were allocated to control groups: 1) when they had physical defects that made them ineligible for anesthesia (*e.g.*, abscessed tooth, arrhythmia, abnormal chest x-ray); 2) when the quota of experimental subjects was filled; 3) in a few when they decided against being anesthetized after the procedure was fully described to them and they had thought it over a few days. Table 1 shows the composition of the groups with respect to age, education, and IQ scores.

Age differences among the groups should not affect the results, since adaptive functioning changes little over the age range encompassed. However, the differences in IQ could produce misleading results. Tests of differences between means (Duncan's new multiple-range test) indicated that the experimental groups did not differ from their own controls, but that the halothane (H) and isoflurane (I) subjects, experimentals (E) and controls (C) alike, differed from one another in both Verbal and Full-scale IQ's. We allowed for these differences statistically in analyzing the results (see below).

Preanesthesia scores on the standard profiled Minnesota Multiphasic Personality Inventory (MMPI)[9] scales also were evaluated. Only one scale, Hysteria, showed significant group differences. The differences were taken into account in evaluating differences in physical symptoms and mood that occurred as a result of anesthesia.

EXPERIMENTAL PROCEDURE

Halothane or isoflurane was administered to experimental subjects in oxygen either with or without 70 per cent nitrous oxide. With nitrous oxide the dosage levels were .5 to 2.0 per cent halothane or .35 to 1.5 per cent isoflurane. Without nitrous oxide, dosage levels were 1.0 to 2.0 per cent halothane or 1.2 to 2.4 per cent isoflurane. Duration of anesthesia was a minimum of 4.4 and a maximum of 8.6 hours, with means of 7.2 hours for halothane and 6.6 hours for isoflurane. Various sensors were attached to the anesthetized subjects' bodies as part of the physiologic study. The halothane and primary isoflurane control subjects were not subjected to anesthesia, or to measurement of physiologic variables, nor were they exposed to the anesthesia laboratory environment. However, supplemental isoflurane controls (isoflurane control 2) entered the laboratory, had most of the sensors attached, and were subjected to inhalation of 0.2–0.3 per cent isoflurane for an average of 60 minutes to allow measurement of subanesthetic uptake of isoflurane. Psychological variables were measured in experimental subjects before anesthesia and 2, 3, 4, 6, 8, and 30 days after anesthesia, and in control subjects at corresponding intervals.

DEPENDENT VARIABLES

Dependent variables included four categories: 1) subjectively evaluated symptoms;

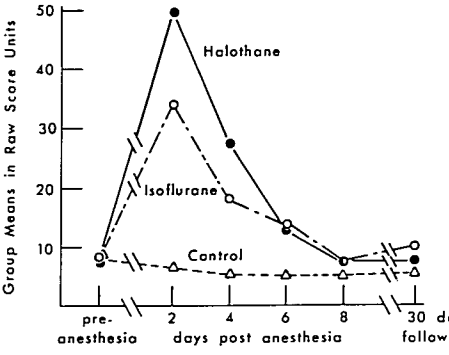

FIG. 1. Effects of halothane and isoflurane anesthesia on somatic and behavioral symptoms. Raw symptom check list scores for somatic and behavioral symptoms following halothane or isoflurane anesthesia were significantly greater than control scores at two and four days. Scores for halothane were greater than isoflurane scores at two and four days.

2) mood; 3) psychiatric symptoms; 4) adaptive functioning (intellectual measures).

It was impossible to evaluate the subjects under double-blind conditions or even with single-blind evaluator ignorance of the group to which the subject belonged. Objectivity of measurement was, however, partially protected by strictly objective scoring of the self-report tests and use of tests of adaptive function that have high established reliabilities.

Subjectively evaluated symptoms were assessed by a 46-item symptom checklist (SCL) designed by the experimenters to reflect symptoms occurring during the two days preceding testing. Items permitted four alternatives of response, weighted 0 to 3 and labelled "not at all" to "extremely." Many of these symptoms had been shown[4] to be altered by cyclopropane anesthesia.

Moods were quantified by the Psychiatric Outpatient Mood Scale (POMS).[9] Respondents rate 70 mood adjectives on a four-point scale yielding scores on seven factor analysis-derived mood variables: Depression, Fatigue, Bewilderment–Confusion, Anger–Hostility, Vigor–Activity, Tension–Anxiety, and Friendliness. The POMS is sensitive to mood states that accompany psychiatric conditions, and closely resembles tests that reflect experimental psychological and physical stress.

The SCL and POMS were administered to all experimental subjects before anesthesia, at 2, 4, 6, and 8 days after anesthesia, and at a 30-day follow-up. Controls took these tests at analogous intervals except that the supplemental isoflurane controls (isoflurane control 2) were not tested at 30-day follow-up.

Psychiatric symptomatology was assessed with the Minnesota Multiphasic Personality Inventory (MMPI),[8] a standardized, published, and widely-used instrument for this purpose. The MMPI was administered to all subjects before anesthesia and to all but isoflurane-supplemental controls at 30-day follow-up.

The complete battery of intellectual measures was: the Wechsler Adult Intelligence Scale (WAIS)[10]; the Wechsler Memory Scale (WMS)[11]; Raven Progressive Matrices, Advanced Form (Raven)[12]; Davis Reading Test, Form 1 (Davis)[13]; Benton Visual Retention Test (Benton)[14]; and Neurological Index of Mental Impairment (NIMI).[15] They measure: verbal and visual–motor psychometric intelligence (WAIS); memory (WMS); abstracting, categorizing, and reasoning ability (Raven); reading comprehension and speed (Davis); memory for geometric forms (Benton); and the NIMI variables listed below. Different forms of the Wechsler Memory Scale, Davis Reading Test, and Benton Visual Retention Test were used. Either the distribution of these different forms was equated for the groups via counter-balanced design or the forms were shown to be equivalent under the conditions of the experiment.

TABLE 2. Probability Levels of Significant Differences in Scores on Symptom and Mood Measures*

	Group Comparisons†	2-day	4-day	6-day	8-day	30-day
SCL	E vs. C	.001	.001	.001	.001§	.01§
	H vs. C	.001	.001	.01	.01§	.05§
	I vs. C	.001	.001	.001	.01§	.01§
	H vs. I	.001	.01	‡	§	§
Depression (POMS)	E vs. C	.001	.001	.01	.01	.05
	H vs. C	.001	.05			
	I vs. C	.001	.001	.01	.01	.01
	H vs. I					.05¶
Fatigue (POMS)	E vs. C	.001	.01	.001		
	H vs. C	.001	.05	.05		
	I vs. C	.001	.001	.001		
	H vs. I	.05				
Bewilderment–Confusion (POMS)	E vs. C	.001	.001	.01		
	H vs. C	.001	.001	.05		
	I vs. C	.001	.01			
	H vs. I	.001				
Anger–Hostility (POMS)	E vs. C	.01	.05	.01		
	H vs. C	.01		.05		
	I vs. C	.05	.01	.05		
	H vs. I	‡				
Vigor–Activity (POMS)	E vs. C	.001§	.01	.05		
	H vs. C	.001§	.05			
	I vs. C	.001§	.01			
	H vs. I	.05				
Tension–Anxiety (POMS)	E vs. C	.001	.01			
	H vs. C	.001	.05			
	I vs. C		.01			
	H vs. I	.01				
Friendliness (POMS)	E vs. C	.001	.05			
	H vs. C	.001				.05¶
	I vs. C	.05				
	H vs. I	.05				.05¶

* One-way analysis of covariance with preanesthesia scores on the same variable as covariate.

† E = pooled experimental subjects; C = pooled control subjects; H = halothane-anesthetized subjects; I = isoflurane-anesthetized subjects.

‡ MAC time used as additional covariate.

§ MMPI-Hy used as additional covariate.

¶ All significant differences except these showed halothane-anesthetized subjects the most distressed, controls the least, and isoflurane-anesthetized subjects intermediate.

All but the NIMI are published tests. The NIMI is a standardized and quantified mental status examination plus some visual–motor and behavior rating items. The subsections of this test we used are: 1) Responsiveness (the examiner's rating of the subject's appearance and test behavior); 2) Verbal Reasoning; 3) Numerical Reasoning; 4) Visual–Motor Functioning. Each subsection includes a number of different types of items. The NIMI also yields a total score and a Mental Impairment Index which is the number of ten possible signs of brain damage produced. Some of these tests were designed to reflect brain damage (*i.e.*, Benton, NIMI, and WMS). Others are direct measures of adaptively significant behavior such as reading ability (Davis) or widely validated measures of intellectual functioning (WAIS).

All ability tests were administered before

TABLE 3. Mean Raw Scores on Symptom and Mood Measures

	Pre	2-day	4-day	6-day	8-day	30-day
SCL						
Halothane	7.4	49.4	27.2	13.0	7.8	7.7
Isoflurane	8.6	34.2	18.0	13.8	7.8	9.8
Controls	8.9	6.9	5.3	5.2	5.0	5.6
Depression (POMS)						
Halothane	5.4	10.8	5.0	4.7	3.1	3.2
Isoflurane	5.2	9.1	8.1	7.1	4.5	6.1
Controls	5.1	2.9	2.1	2.0	2.0	2.3
Fatigue (POMS)						
Halothane	3.9	15.7	7.6	4.9	3.1	4.4
Isoflurane	3.3	11.8	7.6	6.7	2.5	3.8
Controls	4.1	3.6	2.9	2.4	2.6	3.5
Bewilderment–Confusion (POMS)						
Halothane	9.6	15.2	12.1	10.6	8.9	9.0
Isoflurane	9.9	11.9	10.5	9.9	8.2	9.5
Controls	9.8	8.8	8.2	8.4	8.2	8.4
Anger–Hostility (POMS)						
Halothane	3.6	7.6	4.2	4.1	3.1	3.6
Isoflurane	4.7	5.9	6.0	4.6	3.2	4.3
Controls	5.0	3.4	2.7	2.0	2.5	2.5
Vigor–Activity (POMS)						
Halothane	14.4	3.8	10.0	10.9	13.8	13.6
Isoflurane	12.5	6.4	8.7	10.0	12.1	11.2
Controls	11.9	12.2	12.3	11.8	12.6	12.1
Tension–Anxiety (POMS)						
Halothane	11.1	15.1	11.4	10.6	9.1	9.6
Isoflurane	11.9	11.8	11.9	10.7	9.8	10.7
Controls	11.0	9.8	9.2	9.8	9.2	9.5
Friendliness (POMS)						
Halothane	8.8	5.1	7.4	7.9	8.4	9.4
Isoflurane	8.0	6.8	7.0	7.8	8.0	7.1
Controls	8.0	7.9	8.1	7.9	7.4	7.9

anesthesia and at 30-day follow-up. However, practical considerations of resource availability, practice effects, and limitations of subject cooperation prevented readministering some ability tests to all subjects at each of the short-term postanesthesia testing intervals (2 through 8 days).

The NIMI, Davis, and Benton were chosen as the short-term ability battery, administered to different fourths of the experimental groups 2, 3, 4, and 6 days after anesthesia, and to portions of the control groups at comparable times. Since some of the controls were not tested on the exact post-"treatment" date desired, the interval between original testing and post-testing was correlated with change scores on the ability measures to test whether this inconsistency had flawed the design. None of the ability measure change scores was significantly associated with the interval.

Since the isoflurane and halothane experimental groups were not precisely equated for dose and duration of anesthesia, these variables were quantified for subsequent statistical isolation and control. The concentration of anesthetic as a proportion of MAC was multiplied by the duration of exposure at that concentration. The sum of these produced a "MAC time" score for each experimental subject.

METHOD OF ANALYSIS

We used one-way analysis of covariance to control for pre-experimental differences

between the groups. For each dependent variable, preanesthesia scores on the same variable were employed as the covariate. Hysteria (MMPI-Hy) was used as an additional covariate for symptom and mood variables. In comparing the two anesthesia groups, "MAC time" also was evaluated as a covariate and used in those few cases in which it significantly related to a dependent variable. Following calculations of overall statistical significance among groups, individual differences among pairs and groups of means were evaluated with appropriate contrast coefficients. Dependent variables were analyzed by one-way analysis of variance when none of the potential covariates correlated with them; significance among paired means was in these cases evaluated with Duncan's new multiple-range test. Some variables did not possess sufficient variance within some of the cells of the design to permit parametric statistical analysis. In those cases, chi-square or Fisher's exact test were applied to the separate preanesthesia, postanesthesia, and follow-up distributions.

Because of the large number of dependent variables, many of which are intercorrelated, as well as other factors limiting independence of the many statistical tests applied, caution should be used in interpreting the probability values associated with individual outcomes.

Short-term effects on intellectual function after anesthesia were not tested with the same sensitivity as symptoms and moods; only a fourth of each subject group was tested with intellectual measures at each short-term postanesthesia testing period, while every subject, except for missing-data cases, responded to the mood variables and symptom checklist at each postanesthesia testing interval. Due to missing data, N's were sometimes reduced to as few as 22 (instead of 24) in the isoflurance experimental group, 37 (instead of 41) for controls' immediate postanesthesia data, and 29 (instead of 32) for the controls' long-term follow-up data.

Results

The results are described as individual groups showing less ability or more symptomatology than another. This is usually a "shorthand" expression for a significant difference between the groups in postanesthesia scores adjusted for preanesthesia differences by analysis of covariance. Control groups were tested for differences on each dependent variable (adjusted by analysis of covariance) and when not different, combined.

Symptoms and Moods

The symptom checklist (SCL) total score showed the greatest effect of any variable used in the study. This can be seen in table 2; all groups of anesthetized subjects had significantly higher SCL scores than the controls at all short- and long-term follow-up times. Table 2 also indicates that subjects anesthetized with halothane had significantly more symptomatology than isoflurane-anesthetized subjects through 4-day testing. Figure 1 graphically illustrates these major effects. Table 3 shows that by 8-day testing the anesthetized groups were approximately back to their initial SCL levels, even though they remained slightly but significantly more symptomatic than the controls for 30 days after anesthesia.

Of the total 46 SCL items, 39 were significantly affected at 2 days for at least one experimental group, while by 8-day testing only five items were significant for either group. The items most sensitive to anesthesia in general, those differentiating both anesthetized groups from combined controls at $P < .001$ 2 days after anesthesia, were: "Sore throat," "Soreness of muscles," "Smell odor of anesthesia from time to time," "Faintness or dizziness," "Heavy feeling in your arms and legs," "Weakness in parts of your body," "Feeling low in energy or slowed down," "Numbness or tingling in parts of your body," "Increased cough," "Trembling," "Poor coordination," "Nausea or upset stomach not related to motion," "A lump in your throat," "Having to do things very slowly in order to be sure you were doing them right," "Nausea or upset stomach caused by motion," "Sweating," "Tasted anesthesia from time to time," "Drowsiness during the daytime," and "Pains in the stomach."

Differences between halothane and isoflurane appeared greatest at 4 days, with 14

symptoms differentiating controls from halothane subjects but not controls from isoflurane subjects, compared with only four symptoms significantly differentiating isoflurane subjects from controls but not from halothane subjects. Four direct halothane–isoflurane individual item comparisons were significant (halothane subjects more symptomatic in each instance) at 2 days ("Nausea or upset stomach caused by motion," $P < .05$; "Hot or cold spells," $P < .05$; "Poor appetite," $P < .01$; "Vomiting associated with motion," $P < .05$); and four at 4 days ("Smell odor of anesthesia from time to time," $P < .01$; "Weakness in parts of your body," $P < .05$; "Tasted anesthesia from time to time," $P < .01$; "Having to check and double check what you do," $P < .05$). No direct halothane–isoflurane item comparison was significant at 6 or 8 days.

The anesthetized groups differed significantly from controls on only one item before anesthesia and one at long-term follow-up. Those two items, with isoflurane subjects more symptomatic than controls beyond the .05 level, were "Your mind going blank" at initial testing (endorsed by 29 per cent of the isoflurane group!) and "Soreness of your muscles" at longterm follow-up. The anesthetized groups did not differ from each other on any item before anesthesia or at long-term follow-up.

The POMS showed a similar effect of anesthesia (table 2). All scores showed greater dysphoria for combined experimental groups through 4 days after anesthesia; five scores showed this at 6 days, and depression persisted at 8 and 30 days. Five of the seven POMS factors showed significantly more dysphoria produced by halothane than by isoflurane at 2 days, but except for the two reversals at 30 days (Depression and Friendliness), there was no difference between the two anesthetic groups at 4 through 30 days.

In contrast to the generally less severe symptomatology and dysphoria produced by isoflurane compared with halothane, POMS Depression showed an effect lasting past 4 days for the isoflurane group alone, and even through 30 days, when that group rated itself as significantly more depressed than the halothane group as well as the controls.

Intellectual Functions at Short-term Follow-up

The short-term effects on ability are summarized in table 4, which gives the means, and table 5, which gives the statistical significance of differences between the means.

Two days after anesthesia, the combined experimental groups scored below combined controls on Davis reading Level (accuracy of comprehension), Davis reading Speed (speed and accuracy), and NIMI Responsiveness. These effects also held for pooled subjects tested at 2 and 3, 2 through 4, and 2 through 6 days, but not for 3-, 4-, and 6-day groups alone. The combined experimental subjects also scored lower than controls on NIMI Total score at 2 and 3 days combined.

When the groups were evaluated separately, the combined anesthetic groups' effect on Davis Level and Davis Speed also held for halothane; however, isoflurane affected Davis Speed only. Halothane subjects also scored lower than controls on NIMI Responsiveness at 4 days, 2 through 4 days, and 2 through 6 days. Isoflurane subjects scored below controls on this variable at 3 days and 2 and 3 days combined.

Halothane subjects scored below controls on NIMI Numerical Subtotal at 4 days. Isoflurane subjects sometimes scored below controls on the additional NIMI variables: Arithmetic, Visual–Motor Subtotal, and Total Score.

On direct comparisons between the two anesthetized groups, isoflurane subjects sometimes scored higher than halothane subjects on the NIMI variables Responsiveness, Numerical Subtotal, and Similarities and Differences, but halothane subjects scored higher than isoflurane subjects on Davis Level at 6 days. Paradoxically, individuals anesthetized with isoflurane sometimes outscored controls on the NIMI variables Similarities and Differences and Numerical Subtotal.

Intellectual Function at Long-term Follow-up (30 Days Postanesthesia)

Measurement of intellectual function at follow-up was very comprehensive, including the WAIS, Wechsler Memory Scale,

TABLE 4. Mean Scores* on Ability Measures That Showed Significant Short-term Effect

	Adjusted Group Means			
	2-day	3-day	4-day	6-day
Davis Level				
Halothane	76.8	81.2	81.3	87.3
Isoflurane	82.6	84.9	84.6	79.9
Controls	85.0			
Davis Speed				
Halothane	77.5	83.9	83.5	85.1
Isoflurane	81.4	84.7	85.4	83.1
Controls	85.1			
NIMI Responsiveness				
Halothane	13.4	13.8	12.9	13.6
Isoflurane	13.6	13.4	14.6	13.8
Controls	14.1			
NIMI Similarities and Differences				
Halothane	14.2	14.1	14.5	13.9
Isoflurane	14.6	14.4	15.0	15.4
Controls	14.2			
NIMI Arithmetic				
Halothane	15.8	15.8	14.7	14.6
Isoflurane	14.6	16.5	16.6	16.7
Controls	15.9			
NIMI Numerical Total				
Halothane	32.3	32.2	30.0	32.3
Isoflurane	33.1	32.1	34.0	34.0
Controls	32.5			
NIMI Design Recall				
Halothane	18.8	18.6	19.2	18.7
Isoflurane	17.6	17.7	19.5	19.8
Controls	19.0			
NIMI Visual–Motor Total				
Halothane	47.4	47.1	48.2	47.5
Isoflurane	46.4	45.9	48.0	48.0
Controls	47.4			
NIMI Total Score				
Halothane	154.9	155.4	155.2	156.1
Isoflurane	156.1	153.1	159.8	159.1
Controls	157.0			

* Davis means are transformed scaled scores. All other means are in raw score units. Controls' values are for all controls combined across short-term delay periods.

and Raven, in addition to the short-term battery, for a total of 42 variables. On none of them did the anesthetized subjects score significantly below controls. Isoflurane subjects obtained higher scores than halothane subjects on NIMI Similarities and Differences ($P < .05$, two-tailed), but approximately two variables would be expected to differentiate the groups by chance at this probability level. However, paradoxically, anesthetized subjects scored higher than controls on a large number of variables (two-tailed tests). The combined experimental groups outscored combined controls on NIMI Design Recall, Visual–Motor Subtotal, and Sentence Recall (each $P < .05$); on WAIS Digit Symbol, Performance IQ (each $P < .05$), and Full Scale IQ ($P < .01$). The combined experimental

TABLE 5. Probability Levels of Significant Short-term Differences on Ability Measures*

	Group Comparisons†	2-day	3-day	2–3-day	4-day	2–4-day	6-day	2–6-day
Davis Level	E vs. C	.001		.01		.05		.05
	H vs. C	.01		.01		.01		.05
	I vs. C						.05	
	H vs. I						.05	
							I < H‡	
Davis Speed	E vs. C	.001		.01		.01		.05
	H vs. C	.001		.01		.01		.05
	I vs. C	.05						
	H vs. I							
NIMI Responsiveness	E vs. C	.05		.05		.05		.05
	H vs. C				.01	.01		.01
	I vs. C		.05	.05				
	H vs. I				.01			
					I > H‡			
NIMI Similarities and Differences	E vs. C							
	H vs. C							
	I vs. C						.05	.05
							I > C‡	I > C
	H vs. I						.05	
							I > H	
NIMI Arithmetic	E vs. C							
	H vs. C				.05		.05	.05
	I vs. C	.05					.05	.05
							I > C‡	I > C
	H vs. I							
NIMI Numerical Total	E vs. C							
	H vs. C				.05			
	I vs. C							.05
								I > C
	H vs. I				.05			
					I > H‡			
NIMI Visual–Motor Total	E vs. C							
	H vs. C							
	I vs. C			.05				
	H vs. I							
NIMI Total Raw Score	E vs. C			.05				
	H vs. C							
	I vs. C	.05		.05				
	H vs. I							

* Analysis of covariance using initial level on the same variable as covariate. MAC time was never significantly related to the differences, so was not used as a covariate.

† E = pooled experimental subjects; C = pooled control subjects; H = halothane-anesthetized subjects; I = isoflurane-anesthetized subjects.

‡ The notation "<" signifies that the group on the low side of the inequality sign scored lower than the group to the right. For example, "X < Y" means that group X scored below group Y. In all other significant comparisons the anesthetized group scored lower than controls.

groups also scored higher than isoflurane controls on WMS Logical Memory (memory for meaningful prose) ($P < .05$). Isoflurane subjects outscored combined controls on NIMI Cube and Design Recall, and on WAIS Full Scale IQ (each $P < .05$). Halothane experimental subjects scored higher than combined controls on WAIS Digit Symbol

$P < .05$). Performance IQ ($P < .01$), and Full Scale IQ ($P < .05$).

Measures of Personality and Psychopathology at Long-Term Follow-up 30 Days Postanesthesia

No finding could reasonably be attributed to direct effects of anesthesia. Halothane and isoflurane controls differed on the Hypochondriasis scale and on the admission of symptoms component of the Hysteria scale (Hy Ad), $P < .05$. On this latter measure, halothane subjects scored lower than their controls, while isoflurane subjects scored higher than their controls (each $P < .05$). On Tryon's cluster score T-2, Body Symptoms, the controls differed at $P < .05$, while isoflurane subjects scored higher than their own controls, also $P < .05$. These relationships condense to one basic finding: the two control groups differed on measures of admission of bodily complaint 30 days after anesthesia, when these measures are adjusted for preexperimental levels. Isoflurane control subjects indicated less physical symptomatology than did halothane controls.

Discussion

Statistical significance is not necessarily practical significance. However, some of the effects found in this study were large relative to experimental error—so much so that very small groups of anesthetized subjects showed statistically reliable differences from controls on intellectual variables (*e.g.*, the groups of four halothane and six isoflurane 2-day subjects each scored reliably lower than controls on reading speed). Each anesthetic produced enough dysphoria, physical symptoms, and intellectual impairment four days after anesthesia to warrant advising patients against undertaking efforts requiring maximum intellectual competency during that interval. The specific symptoms and types of intellectual deficits recorded provide a basis for counseling patients about what to expect simply as a result of being anesthetized by *these* anesthetics for 4.4 to 8.6 hours. These symptom data also provide additional information to help distinguish between postanesthesia effects *per se* and postoperative complications. However, more detailed study of the postanesthesia period from recovery of consciousness to approximately four days after anesthesia is needed to provide the most useful clinical information of this type. With increased outpatient surgery, comprehensive description of immediate postanesthetic effects of the most commonly employed anesthetics is essential.

Concerning the nature of the intellectual deficits recorded, they were not of the magnitude typically associated with clinically significant brain damage, nor was there evidence of pathognomonic signs of brain damage as a result of anesthesia. Instead, there was a slight impairment of variables covering the complete spectrum of intellectual functions measured.

No intellectual deficit attributable to anesthesia was detected 30 days after anesthesia. In fact, anesthetized subjects tended to out-perform controls at that time. This is reassuring with respect to the ultimate benign effects of these anesthetics. The higher ability scores of the anesthetized subjects 30 days after anesthesia constitutes an enigma. We do have anecdotal evidence that by this final testing period control subjects were becoming more impatient with the oft-repeated testing than were the anesthetized subjects. Scores on ability tests typically increase slightly on repetition due to practice effect; the decline of control scores 30 days after anesthesia compared with their initial values supports an interpretation of decreased effort at that time. The experimental subjects may have sustained their motivation due to their having experienced an anesthesia-produced period of decreased functioning, thus finding the 30-day-postanesthesia testing a challenge to improve their performance. The same effect might account for the paradoxical outscoring of controls by isoflurane-anesthetized subjects on some intellectual variables six days after anesthesia.

This hypothesis about the relatively poor showing of the controls on long-term follow-up postulates confounding of practice effects, which in ability measurements typically cause increased scores, and lessened motivation to perform in that group. Our data do not permit disentangling the two. How-

ever, such effects could not have any bearing on the differences between experimental groups, and with respect to short-term follow-up would have served only to diminish experimental–control group differences.

We do not believe that the anesthetized subjects were more symptomatic 30 days after anesthesia as a lingering direct effect of the anesthetics. More likely, the experience of being anesthetized combined with training to report symptoms led to increased body awareness, which was reflected in the tiny but statistically significant persistence of symptoms and dysphoria 30 days later. However, it is possible that some specific symptoms of anesthesia linger that long.

The two anesthetics produced different effects on symptoms, mood, and intellectual function. However, receipt of nitrous oxide in conjunction with the other anesthetics could be hypothesized to account for these differences. Half of the halothane-anesthetized subjects, but only a third of the isoflurane-anesthetized subjects, also received nitrous oxide. We did not anticipate this as a design factor, with the consequence that this inequality and extreme inequality of distribution of nitrous oxide recipients over post-anesthesia test days occurred. There was no halothane–nitrous oxide recipient at 3 days, no isoflurane–nitrous oxide recipient at 4 days, and all 6-day halothane subjects received nitrous oxide.

Some, but not all, of the differences between halothane and isoflurane correlate with the proportion of anesthetized subjects receiving nitrous oxide. Isoflurane subjects, but not halothane subjects, scored below controls on four comparisons of intellectual variables at 3 days or 2 and 3 days combined; half of the isoflurane subjects, but only a fourth of the halothane subjects, received nitrous oxide in the combined 2- and 3-day group.

To test the possible nitrous oxide effect, it was necessary to combine adjacent groups, with consequent loss of design precision and sensitivity. Analyses of covariance (preanesthesia scores on the same variable as covariate) in a 2×2 halothane versus isoflurane, nitrous oxide versus no nitrous oxide, design were done for all variables showing halothane versus isoflurane differences.

These analyses show that part, but not all, of the halothane-versus-isoflurane differences could be attributable to nitrous oxide. The six halothane-versus-isoflurane SCL mood differences 2 days after anesthesia reduced to three at $P < .05$ (SCL, Tension, and Bewilderment) and one at $P < .10$ (Vigor). Nitrous oxide produced a reduction of Vigor 2 days after anesthesia ($P < .05$). There was no nitrous oxide effect on mood or symptoms 4, 6, or 8 days after anesthesia. The halothane-versus-isoflurane intellectual differences also were reduced in number with this less sensitive analysis. Still, the isoflurane-anesthetized subjects achieved higher scores than halothane-anesthetized subjects on four comparisons (three at only $P < .10$, one at $P < .05$), while the subjects receiving nitrous oxide scored lower than those who did not on NIMI Responsiveness 3 and 4 days after anesthesia combined ($P < .02$). No interactive effect of nitrous oxide and the other anesthetics was detected.

When the effects that could have been due to nitrous oxide are isolated, there remain differences in mood and symptoms showing halothane more potent than isoflurane in producing changes in these variables. However, only minimal effects on intellectual function remain. Future comparisons of halothane and isoflurane, as well as other anesthetics, should eliminate nitrous oxide or include it as a design factor.

The differences favoring isoflurane may be explained on two bases. Isoflurane is less soluble than halothane, and its elimination is therefore more rapid.[16] In addition, metabolism of isoflurane is far less than metabolism of halothane.[17]

MAC time related to few of our variables. It would be unjustified to generalize from this to other conditions such as different levels, types and durations of anesthesia, or to clinical conditions under which subjects are additionally stressed.

The mechanisms causing reduced mental functioning following anesthesia require clarification. Are these intellectual deficits merely the result of the distraction of the somatic distress experienced, or are they a more direct function of disturbed brain physiology? We used the SCL difference score as an additional covariate with our most sensitive intellectual measures, Davis

Level, Davis Speed of comprehension, and NIMI Arithmetic. When the variance associated with SCL difference scores was thus removed from these intellectual variables, there was no residual effect due to anesthesia. However, this does not prove that the intellectual effects were merely reactions to the experienced physical distress; both could be caused by some central factor with the same result. Direct investigation of the contribution of physical distress might require methods such as experimentally inducing nausea and other physical distress comparable to that produced in this study but independently of central nervous system dysfunction to see whether comparable intellectual deficit results.

There is evidence that mental impairment following anesthesia is not merely caused by reaction to physical distress. Bruce, Bach and Arbit[18] found that four-hour exposure to 15 ppm halothane plus 500 ppm nitrous oxide increased reaction time, decreased vigilance, and decreased short-term memory. These anesthetic concentrations were so low that the subjects could not discriminate this exposure from the control condition of breathing pure air. Though somnolence was more common in the anesthetic-exposure condition, no nausea or other distress was reported. These effects were found immediately after exposure had been terminated and are presumably the direct effects of minute residual levels of the anesthetics in the subjects' bodies. Drummond[19] suggests that trace amounts of anesthetics may remain in the body long after recovery of consciousness, producing decrements in mental function in proportion to their concentrations. Drummond also suggests an alternative mechanism of postanesthetic reduction of mental function via reduction of catecholamine metabolism by anesthesia.

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