Narcotic Effects in Man of Breathing 80-20 Argon-Oxygen and Air under Hyperbaric Conditions

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FOWLER, B., AND K. N. ACKLES. *Narcotic effects in man of breathing 80-20 argon-oxygen and air under hyperbaric conditions.* Aerospace Med. 43(11):1219-1224. 1972.

The qualitative and quantitative effects of breathing 80-20 argon-oxygen and air were compared at the surface and at 4 and 7 ATA with 10 subjects using three measures—mental arithmetic, subjective estimates of narcosis and an adjective checklist. Both the mental arithmetic task and the subjective estimates of narcosis indicated that the argon-oxygen mixture was more narcotic than air. The adjective check list revealed that similar types of adjectives were used to describe the subjective effects of both mixtures and that these choices corresponded to previous descriptions of narcosis. There was also evidence that factors other than internal subjective cues influenced the subjects' estimates of narcosis, the major one being feedback from performance on the arithmetic test. It was concluded that the qualitative effects of argon and nitrogen were the same on the various measures of narcosis but the discrepancy between the dose response functions for various measures found by a comparison of the present results and those of other studies of nitrogen narcosis in humans raises questions about the usefulness of quantitative differences between the inert gases as indicators of underlying causal mechanisms of narcosis.

THE TERM "INERT GAS NARCOSIS" refers to the common supposition that breathing the so-called inert gases results in behavioral effects which are qualitatively identical but quantitatively different, i.e., the narcotic syndrome is identical for each gas but at the same partial pressure in the breathing mixture different gases will affect any given measure to different degrees. Experiments, in which the effects on behavior of two or more inert gases have been compared, have been aimed at establishing the relative narcotic potency of the gases and it has been assumed that their qualitative effects are identical. As a result, there is a virtual absence of studies in which a comparison of effects can be made. In studies using animals[9,19,20] gross measures concerned with a behavioral end-point, unconsciousness, have generally been used. Consequently, these studies give no information about the graduated effects of the gases prior to unconsciousness. Studies involving human subjects in which the effects of two inert gases have been compared also offer little help. In some instances, one or both of the gases turned out to lack narcotic properties at the pressure level used in the experiment.[7,14,16] In other studies, the indices of narcosis have been insufficiently precise to allow adequate comparisons to be made.[12] Behnke and Yarbrough[6] reported a study in which the effects of 69% argon- 11% nitrogen-21% oxygen were compared with air. Four experienced divers were compressed once each in a wet compression chamber to a pressure which varied in individual cases between 4 and 5 ATA and were asked to estimate their depth. They were unable to detect any subjective difference between the mixtures at the surface but tended to overestimate their depth by a factor of approximately two while breathing the argon mixture under pressure. Unfortunately, in the latter condition there was no control condition in which air was breathed. Nevertheless, Behnke and Yarbrough concluded that argon was more narcotic than nitrogen.

The purpose of the present study was to compare the qualitative and quantitative effects of argon and nitrogen, using three measures of narcosis. The first was a performance measure, mental arithmetic. The second was a subjective estimate by each subject of his degree of narcosis. The use of this measure was suggested by the work of Frankenhaeuser,[15] who reported that reliable estimates of nitrous oxide intoxication can be made at ground level. The third measure was an adjective checklist. It was hoped that such a list would provide more precise information than that currently available about the kinds of subjective sensations associated with narcosis.

MATERIALS AND METHODS

There were two experiments. In the first, arithmetic performance, subjective ratings of the degree of narcosis and responses to the adjective checklist were determined for 10 subjects at the surface (1 ATA) and at 4 and 7 ATA breathing both air and an 80-20 argon-oxygen mixture. In the second experiment, arithmetic performance of eight subjects was measured at the surface (1 ATA) and at 5.5 and 10 ATA, breathing air. Six

The authors gratefully acknowledge the technical assistance of Gillian Dalton and Orest Burak at all stages of this research.
DCIEM Research Paper No. 855.
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subjects were common to both experiments. All subjects were experienced divers from the Defence and Civil Institute of Environmental Medicine.

Measures of Narcosis—The mental arithmetic task used in this study has been previously described by Ackles and Fowler.[1] Ratings of the degree of narcosis were obtained by the method of magnitude estimation. Subjects were instructed to estimate numerically in writing their degree of narcosis by reference to an arbitrary number, 10, designated as the "normal" state just prior to the experiment. The size of the reported number was to be in direct proportion to the increase in the degree of narcosis. For example, if a subject estimated that his degree of narcosis has increased by 100%, then he reported the number 20, or if the estimated increase was 10%, he reported 11. To aid recall of the scaling system, a chart illustrating the relations between degree of narcosis and the numbering system was used by each subject each time a rating was made.

TABLE I. THE EXPERIMENTAL DESIGN USED IN THE FIRST EXPERIMENT INDICATING THE GAS MIXTURE BREATHED FIRST AT EACH DEPTH AND THE ORDER OF DEPTHS

pressure	1 ATA	4 ATA	7 ATA	1 ATA
S1	air	air	argon	air
S2	argon	argon	air	air
S3	argon	air	air	argon
S4	air	argon	argon	air
S5	argon	argon	air	argon
pressure	1 ATA	7 ATA	4 ATA	1 ATA
S6	air	air	argon	argon
S7	argon	argon	air	air
S8	argon	air	argon	air
S9	air	argon	air	argon
S10	air	argon	air	argon

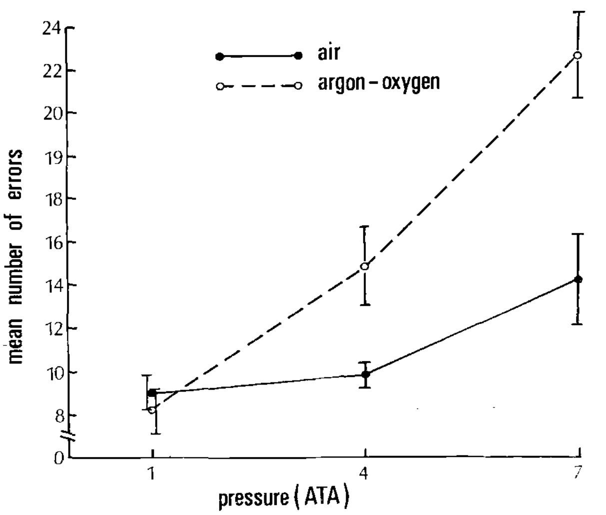

Fig. 1. The mean number of errors in arithmetic performance as a function of breathing mixture and pressure. The vertical bars indicate the standard error of the mean.

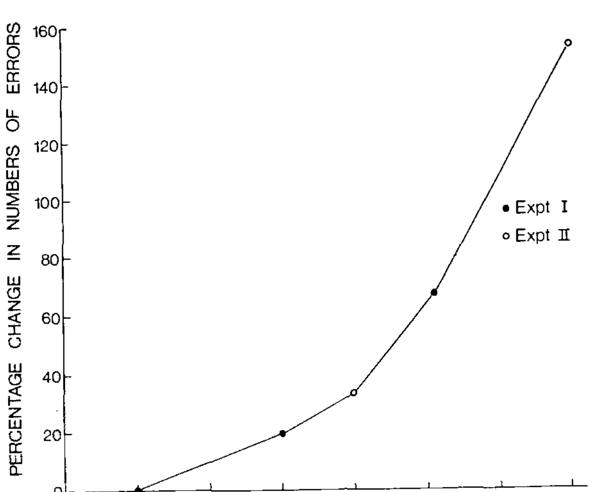

Fig. 2. The mean percentage changes in arithmetic performance as a function of pressure breathing air.

The adjective checklist was composed of 41 adjectives in alphabetical order taken from a longer list used by Wendt and Cameron[25] for assessing the subjective effects of drugs. The adjectives chosen included many thought to be relevant to subjective changes associated with the narcotic state and the hyperbaric environment. In addition, the colloquial expression "narced," used by divers to describe narcosis, was included. On each occasion that the adjective checklist was presented to a subject, one of the following five descriptions had to be checked for each adjective using the normal state as a reference: (1) definitely less, (2) slightly or possibly less, (3) have not changed or cannot decide, (4) slightly or possibly more and (5) definitely more.

Design and Procedure—The design of the first experiment, summarized in Table I, has been described by Ackles and Fowler[1] where it is referred to as Series I. At each combination of pressure and gas mixture, the tasks were presented in the following order: (1) first narcosis rating, (2) adjective checklist, (3) mental arithmetic, (4) second narcosis rating and, after a five-minute period during which a physiological measure was taken, (5) third narcosis rating. In addition, after each narcosis rating each subject was asked to decide which gas mixture was being breathed. At no time during the experiment was a subject told which gas mixture was being breathed and the experimental procedure was arranged so no cues identifying the gas mixture were available to a subject.

A subject, seated in the pressure chamber, was instructed on each task and given several practice lists of the arithmetic test while breathing air through an oral-nasal mask. The subject then breathed one of the two mixtures for two minutes, after which the series of tasks was presented. The gas mixture was then changed and the entire procedure repeated. When the surface tests were completed the chamber was secured for diving and pressurized for the same tests at 4 and 7 ATA. During compression (4 ATA/min) and decompression (2.8 ATA/min) the mask was removed but was donned again two minutes after the appropriate pressure level had been reached. This time period allowed the temperature in the chamber to stabilize. Because of decompression schedule requirements, the post-dive tests at the surface were conducted about three hours after the final test at pressure.

In the second experiment, eight subjects were tested in pairs at the surface (1 ATA) and at 5.5 and 10 ATA on the mental arithmetic task while breathing air through an oral-nasal mask. Half the pairs were tested in the order 1, 5.5, 10 ATA and half in the order 1, 10, 5.5 ATA. Three arithmetic tests were used, each pair being presented with a different list at each pressure in partially counterbalanced order.

RESULTS

Arithmetic Performance—Arithmetic performance for the first experiment, in terms of the mean number of errors with respect to gas mixture and pressure, is illustrated in Figure 1. Data from the post-dive controls have been omitted because *t* tests showed there was no significant difference from the pre-dive controls. Inspection of Figure 1 indicates that the number of errors increased with increasing pressure, breathing either air or argon-oxygen, but that this increase was greatest for the latter mixture. These differences were confirmed by a repeated measures design analysis of variance[18] consisting of 10 subjects x 2 gas mixtures x 3 pressures, which showed that the effects of pressure ($F = 24.66$; $df = 2,18$; $p<0.01$) and gas mixture ($F = 16.24$; $df = 1,9$; $p<0.01$) were significant, as was the pressure x gas mixture interaction ($F = 6.39$; $df = 2,18$; $p = 0.05$). Figure 1 also suggests that the decrement in performance with increasing pressure is a curvilinear function. This suggestion was further examined by combining the results of the second experiment, in terms of the mean number of arithmetic errors, with those from the first experiment (Figure 2). The change in performance at each pressure is shown as a percentage of the appropriate surface control so that both sets of data can be compared directly. These data confirm the curvilinearity of the arithmetic performance function.

Narcosis Ratings—The mean narcosis ratings for each combination of gas mixture and pressure are illustrated in Figure 3. Once again, there was no significant difference between the pre- and post-dive controls and the latter have been omitted. Table II shows the SEM's (standard error of the means) for each of the means plotted in Figure 3. Inspection of Figure 3 indicates that the magnitude of the ratings increased with increasing pressure breathing either air or argon-oxygen, but that this increase was greater for the latter mixture. In addition, with the exception of the 4 ATA air breathing condition, there was a systematic difference in the magnitude of the three ratings. The second rating, made after the arithmetic test, was greater than the first rating made before the test, while the third rating fell between the two. These differences were confirmed by a repeated measures design analysis of variance consisting of 10 subjects x 2 gas mixtures x 3 pressures x 3 ratings which showed pressure ($F = 39.73$; $df = 2,18$; $p<0.001$) gas mixture ($F = 12.63$; $df = 1,9$; $p<0.01$) ratings ($F = 6.48$; $df = 2,18$; $p<0.01$) and the pressure x gas mixture interaction ($F = 26.28$; $df = 2,18$; $p<0.001$) were significant. There is also some indication in Figure 3 that the magnitude of the difference between successive ratings was greater when breathing argon-oxygen than when breathing air, but the gas mixture x ratings interaction did not achieve an acceptable level of significance ($F = 3.32$; $df = 2,18$; $0.05 > p < 0.10$).

An examination of the relation between arithmetic performance and the estimates of narcosis revealed that narcosis estimates made immediately after the test paralleled the pattern of arithmetic performance in certain ways which are not apparent in ratings made before the test. This can be seen in the air breathing condition where there was no significant difference between the surface control and 4 ATA for both arithmetic performance and rating 2. However, there was a difference for rating 1 ($t = 3.07$; $df = 9$; $p<0.02$). The parallel is also evident at 4 ATA, where there was a significant difference between argon-oxygen and air for arithmetic ($t = 3.30$; $df = 9$; $p = 0.01$) and for rating 2 ($t = 2.99$; $df = 9$; $p<0.02$) but not for rating 1.

The closer relation between arithmetic performance and the second ratings compared to the first is also apparent in a shift in the direction of the correlation between the two measures. Pearson product-moment correlation coefficients were calculated between arithmetic performance and rating 1 and 2 for air and argon-oxygen separately ($N = 30$). For rating 1 and 2 respectively, $r = 0.255$ (*ns*) and 0.328 ($0.05 > p < 0.10$) breathing air, $r = 0.558$ ($p<0.01$) and 0.634 ($p < 0.01$) breathing argon-oxygen. It should be noted that the correlations for air are of questionable validity due to the restricted range of scores. A relatively high proportion showed little of no change from the surface control due to the lack of a narcotic effect at 4 ATA.

Adjective Checklist—The first analysis of the adjective checklist is shown in Table III, which shows the to-

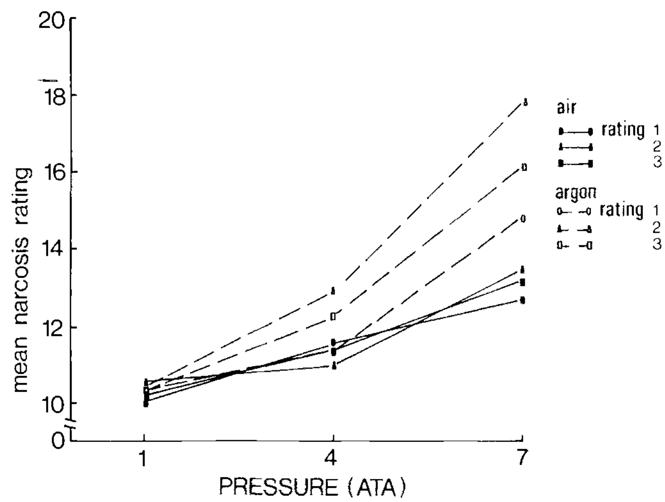

Fig. 3. Mean narcosis ratings as a function of breathing mixture and pressure.

TABLE II. STANDARD ERROR OF THE MEANS FOR THE NARCOSIS RATINGS IN EACH CONDITION REPRESENTED IN FIGURE 3

	1 ATA		4 ATA		7 ATA	
	AIR	A-O_2	AIR	A-O_2	AIR	A-O_2
RATING 1	± .01	± .25	± .51	± .51	± .70	± .83
2	± .30	± .25	± .50	± .78	± .76	±1.50
3	± .20	± .25	± .63	± .73	± .70	± .97

tal number of adjectives checked for each combination of pressure and gas mixture. Table III indicates that the total number of responses increased with increasing pressure, with the exception of the "slightly or possibly less" category for argon-oxygen at 7 ATA. In addition, there was a clearcut increase in the total number of responses to the "definitely" category at 7 ATA, although there was not a consistently greater number of responses at a given pressure for the argon-oxygen mixture.

The second analysis, illustrated in Table IV, identifies those adjectives which were checked by three or more subjects. These data have been summed across the categories "slightly" and "definitely" as a result of the low absolute frequency of response (presumably due to the relatively small number of subjects used for a task of this nature) and some caution must therefore be exercised in interpretation. One indication of unreliability is given by the fact that not all the subjects responded to the adjective "narced" at 7 ATA. In the category "more" two types of adjectives are identifiable. One type appears to relate to the state of consciousness and includes "light-headed," "confused," "fuzzy" and "hazy." The second type refers to feelings of euphoria and includes "genial," "carefree" and "cheerful."

In the category "less" two other types of adjectives can be distinguished. One type refers to a loss of work capabilities and includes "effective" and "efficient" while the other category is less clearly defined but might be described as referring to lowered inhibitions and includes "cautious" and "self-controlled." In general, there is a fairly high degree of commonality among the types of adjectives used to describe the effects of each gas mixture.

It was also determined from an analysis of the adjective checklist data that the accuracy of identifying the gas mixture did not increase either as a function of the three successive choices or of increasing pressure. However, it was established that three subjects chose the correct breathing mixture more often than would be expected by chance (the binomial test gave $p = 0.035$ for each of these subjects and $p > 0.05$ for all other subjects). As a result of informal post-experimental interviews, it was determined that two of the three subjects who performed at a level greater than chance chose between the mixtures on the basis of a characteristic odor which was reported to be noticeable when first breathing the argon-oxygen mixture.

TABLE III. TOTAL NUMBER OF RESPONSES IN EACH CATEGORY OF THE ADJECTIVE CHECK LIST FOR EACH BREATHING MIXTURE AND PRESSURE CONDITION. FOR EACH ADJECTIVE THE SUBJECTS MATCHED THEIR SUBJECTIVE FEELINGS WITH ONE OF FOUR POSSIBLE CATEGORIES; 1) SLIGHTLY OR POSSIBLY MORE; 2) DEFINITELY MORE; 3) SLIGHTLY OR POSSIBLY LESS; 4) DEFINITELY LESS

	More				Less			
	Slightly or Possibly		Definitely		Slightly or Possibly		Definitely	
ATA	Air	Argon	Air	Argon	Air	Argon	Air	Argon
1	5	10						
4	33	41	3	2	17	24	2	8
7	49	46	19	15	30	22	12	14
1	6	5			2			

TABLE IV. MOST FREQUENTLY CHECKED ADJECTIVES IN THE CATEGORIES "MORE" AND "LESS" FOR EACH BREATHING MIXTURE AND PRESSURE (*f* REFERS TO THE TOTAL NUMBER OF RESPONSES)

MOST FREQUENTLY CHECKED ADJECTIVES MORE

AIR—4 ATA	f	ARGON—4 ATA	f
'narced'	5	'narced'	5
confused	3	lightheaded	4
		confused	3

AIR—7 ATA	f	ARGON—7 ATA	f
'narced'	7	carefree	5
lightheaded	6	lightheaded	5
fuzzy	4	'narced'	4
genial	4	numb	4
carefree	3	cheerful	4
cheerful	3	dizzy	3
elated	3	hazy	3
		tingling	3

MOST FREQUENTLY CHECKED ADJECTIVES LESS

AIR—4 ATA		ARGON—4 ATA	f
		effective	4
		efficient	3

AIR—7 ATA	f	ARGON—7 ATA	f
cautious	4	efficient	4
anxious	3	effective	4
effective	3	cautious	4
self-controlled	3	annoyed	4

DISCUSSION

Both nitrogen and argon affected the arithmetic and the subjective estimates similarly, confirming the conclusion of Behnke and Yarbrough[6] that argon is more narcotic than nitrogen. It is not possible to compare relative narcotic potency more precisely between the two indices because identical units are not used for the dependent measures. In most animal studies of narcosis pressure or depth is used as the dependent variable so that a common frame of reference is achieved. Similarly, Behnke and Yarbrough used subjective estimates of depth and on the basis of their results a number of writers[7,9,19,21] have concluded that argon is twice as narcotic as nitrogen. This generalization may not be warranted because subjective estimates of depth most probably do not bear a one-to-one relationship with actual depth.[23]

The arithmetic task and the subjective estimates also provide some information about the dose-response functions of each gas although the present experiment was not designed to investigate this point in detail. Qualitative similarity of the effects of the gases implies that the dose-response functions will be related. In the case of the arithmetic test a curvilinear function most probably exists for both gases. In the case of the subjective estimates the results are not clear-cut; for rating 1 breathing air a linear function is apparent, while in the argon beathing condition it would appear to be non-linear.

However, extension of the pressure range over which estimates are made would probably result in a non-linear function for nitrogen as well as argon. The fact that rating 2 breathing air shows greater similarity to the argon breathing condition most probably reflects the influence of the level of performance achieved on the arithmetic test and will be discussed later.

There appear to be no previous experiments in which dose-response functions for two gases have been compared simultaneously, but data from experiments in which nitrogen dose-response functions have been investigated indicate that the shape of the function depends on the particular measure of narcosis or even different forms of the same measure. Linear functions have been found for reaction time,[22] free association[2] and mental arithmetic[3,8] while curvilinear functions have been found for digit cancellation, visual reaction time,[22] mental arithmetic and two kinds of manual dexterity.[2] The foregoing results demonstrate that neither the assumption of linearity (implied by the use of a simple numerical index to describe relative narcotic potency[7]) nor the assumption of non-linearity[17] is wholly adequate as a description of the dose-response functions produced by the inert gases.

A minimal requirement for demonstrating the qualitative similarity of nitrogen and argon involves demonstrating that some behavioral measures are affected by both gases while others are not affected by either gas. In principle, the adjective checklist is a particularly efficient means for comparing qualitative effects because each adjective can be regarded as a separate measure of narcosis and consequently it should be possible to demonstrate both the presence and absence of narcotic effects. On the other hand, its disadvantage lies in an inherently high degree of variability. The results obtained indicate that a common pool of adjectives was used to describe the effects of both gases and that these adjectives could be classified into types labelled as "state of consciousness", "euphoric" and "lowered inhibitions" which correspond to the generally recognized effects of nitrogen narcosis.[5,11] The lack of evidence of any ability of the subjects to decide which mixture they were breathing on the basis of the narcotic effects of the gases is consistent with their choice of a common pool of adjectives. These findings support the view that both argon and nitrogen produce qualitatively identical effects. The fourth type of adjective, which was identified with "loss of work capabilities," implies a degree of insight into the effects of narcosis which is not consistent with the usual descriptions of a narcotized person, i.e., overconfidence and an unwillingness to admit to any loss of efficiency.

There is some evidence that the subjective estimates were influenced by factors other than the internal cues associated with narcotic effects. The change in the mean values and the degree of correlation between ratings 1 and 2 so that the latter correspond more closely to the pattern of arithmetic performance suggests that the subjects modified their estimates as a result of feedback from their performance during the test. The source of this feedback probably stems from the fact that performance decrements on the arithmetic test were evident as a failure to complete items rather than as errors in completed items and were therefore obvious to the subject. There is also rather weaker evidence that a second factor also influenced the estimates. On the one hand, at 4 ATA the two mixtures can be discriminated on the basis of the arithmetic test but not the first narcosis rating, which suggests that the latter is less sensitive as an indicator of narcosis. On the other hand, there was a difference between the surface control and 4 ATA breathing air for rating 1 but not for arithmetic, although this difference disappears with rating 2. This apparent contradiction can be resolved if it is hypothesized that this difference reflects a component of the estimate which is based on the subjects' knowledge of the pressure at which the tests were conducted. The reason for rating 3 falling between ratings 1 and 2 is not clear but may be due to forgetting. In any event, the general downward shift in the estimates in rating 3 tends to rule out the possibility that the upward trend in the magnitude of the second ratings was due to a change in the degree of narcosis in the 6-min period between ratings 1 and 2.

The results of the present study, together with the evidence from other studies of nitrogen narcosis discussed earlier, indicate that complex relationships exist among different measures of narcosis. This conclusion has particular relevance for that line of research which seeks to establish a causal relation between relative narcotic potency and some physical parameter of the inert gases. As a general rule, evidence for the hypothesized relation depends largely on demonstrating a correlation between relative narcotic potency and the physical parameters in question.[13] The index of behavior commonly used in these studies, the point of unconsciousness, is assumed to be representative of both the dose-response function for the continuum of consciousness as well as the various other possible measures of narcosis. Thus, the correlational approach assumes that different points on the dose-response function for any particular measure of narcosis, as well as all possible measures of narcosis, would both show invariant correlations with any given physical parameter of the inert gases. If this were not the case, then any explanation for narcosis based on a single point from one measure could hardly be said to have any generality. These assumptions have not been tested directly and the evidence discussed above derived from human studies casts some doubt on their validity.

In a recent review on pharmacological receptors Waud[24] has outlined some of the problems encountered in attempts to relate the production of some effect with the underlying drug-receptor reaction. These problems center around difficulties in inferring the actual relations connecting the two events on the basis of a relation derived from the dose-response function due to the latter's inherent generality. It may be that similar obstacles confront attempts to discover the mechanisms of narcosis through correlative methods since it is apparent that complex and little understood relations intervene between the cause of narcosis at the physico-chemical level and behaviour.

It has often been stated[4,7,10,13] that it is difficult to define terms such as anesthesia and narcosis in any but the vaguest sense. This may be the case at present, nevertheless, this problem must be faced, for it seems that a precise understanding of the qualitative effects of the inert gases is a necessary first step in attempting to clarify the extent to which their quantitative effects can be used to deduce underlying causal mechanisms. This means that not only must the kind of inert gas be varied experimentally, but also its partial pressure on a variety of measures representing different aspects of the narcotic syndrome. This view is directly opposed to that offered by Miller, Paton and Smith,[20] who have suggested that the use of more than one measure of relative narcotic potency handicaps a comparison of results from different studies. It is more likely that establishing a consensus on the use of a single measure would only postpone the need for validating the assumptions underlying the correlational approach.

In conclusion, the present study offers some support for the hypothesis that the inert gases exert qualitatively identical effects although it is clear that the range of measures as well as their degree of sophistication should be extended in future work. The problem of appropriate behavioral models for the analysis of narcosis is treated more fully elsewhere by Fowler.[14] It will also be necessary to examine inert gases that are narcotic at atmospheric pressure. It may be significant that the effects of breathing xenon and krypton at the surface[12] do not bear a strong resemblance to the striking disturbances reported for air at 13 ATA,[2] a pressure difference which might be expected to result in equivalent qualitative effects. It is also evident that the traditional view of a narcotized person, who is seen as incapable of assessing adequately his state of functioning, is not necessarily correct. The subjective ratings demonstrate that consistent responses are possible and, in addition, a fairly strong relation exists between arithmetic performance and the subjective estimates. These findings raise questions about the degree to which divers can be trained to use subjective symptoms of narcosis as an indicator of decrements in skilled performance.

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