THE EFFECT OF INHALING DILUTE NITROUS OXIDE UPON RECENT MEMORY AND TIME ESTIMATION

J. G. ROBSON, B. DELISLE BURNS, AND P. J. L. WELT¹

THE STAGE OF ANALGESIA with amnesia which occurs with the inhalation of anaesthetic agents was recognized very soon after the introduction of ether. John Snow (1) described analgesia as the second degree of narcotism in which the pain of surgical operations was usually not felt. If there were responses to painful stimuli, they were either not remembered or recollected as having occurred in a dream. It is also of interest to note that he did not think it was necessary to maintain deeper anaesthesia for the greater part of protracted operations.

The recent work of Summerfield and Steinberg (2) has made it clear that relatively small quantities of nitrous oxide in the inspired air can interfere with the establishment of new memories. By testing the ability of human subjects to learn nonsense syllables, they have demonstrated that inhalation of a mixture of 30 per cent nitrous oxide in oxygen retards the learning process; at the same time, the presence of the anaesthetic appears to lock previous memory traces into the nervous system so that information acquired prior to the administration of nitrous oxide is forgotten less rapidly than it is by subjects breathing air.

We undertook our own experiments upon the effects of light nitrous oxide anaesthesia for two reasons, the one academic and the other practical. In the first place, it seemed that an investigation of any controllable procedure that interfered with learning might ultimately reveal something of the nature of learning mechanisms at the cellular level. Secondly, the current practice of combining light general anaesthesia with muscular relaxants has raised the question—how light should the anaesthetic be? It seems clear that the only requirement from the patient's point of view is that anaesthesia should be sufficient to produce amnesia for the period of operation. Artusio (3) has described the stage of amnesia produced by the inhalation of diethyl ether and its use in major cardiac surgery.

Our first attempts to investigate the influence of N₂O on the learning process were made in 1956. We were, therefore, unaware of the work of Summerfield and Steinberg (2) which was published in 1957. In this publication they showed clearly that the effect of N₂O on subjects learning nonsense syllables was to decrease the rate and to increase the retention of learning. These observations were entirely consistent with our own preliminary findings and we therefore turned our attention to other effects of N₂O inhalation. Thus the majority of the experimental results reported below describe a disturbance induced by nitrous oxide in estimates of the passage of time by human subjects and cats. Nevertheless those few

¹From the Wellcome Research Department of Anaesthesia and the Department of Physiology, McGill University, Montreal.

experiments concerned with amnesia that we had completed are included in this report.

METHODS

The Administration of Nitrous Oxide

Nitrous oxide and oxygen were administered from a standard Boyle's anaesthetic machine. A non-rebreathing system was provided by means of a Stephen-Slater valve placed close to a standard rubber face-piece. This face-piece contained a small microphone (unless a microphone, amplifier, and loudspeaker were used, it was difficult to understand the subject's speech).

Subjects

Twelve subjects were used for the experiments described in this and the succeeding (4) paper. There were two female subjects, and the ages of all subjects lay between 27 and 44 years.

Estimation of Time by Cats

A gas-tight box 12 in. high, 30 in. long and 12 in. wide was constructed; one wall of this box was transparent. The inner floor on which the cat walked was made of parallel brass strips of 1/8 in. separated by 1/8 in. spaces. A control unit was constructed to supply either half of the floor with sinusoidal 60 c.p.s. voltage between alternate metal strips; the current drawn by the cat could be measured and was approximately the same for all tests. The current used for these tests was sufficient to make the animals seek the unelectrified half of the floor, but was not enough to stop the cat purring.

The cats were trained to cross the midline of the box any time between the fifteenth and thirtieth second measured from the time at which they last crossed. If they tried to cross too early they encountered an electrified floor; if they stayed on one side for too long that side was electrified. The animals chosen for training were young cats of about 1 kg. Training was continued until they would cross the midline ten to fifteen times consecutively without error. Thus the experiments, the results of which are illustrated in Table III, were performed with cats crossing voluntarily and without any reinforcement. The required gas mixtures were supplied to the box through a half-inch pipe let into the floor. Before each exposure of the cat the box was flushed for 10 min. with the required gas mixture flowing at 10 L./min.

RESULTS

Effects of Light Anaesthesia upon Recent Memory in Human Subjects

The Effects of 20-45 per cent nitrous oxide in oxygen. We have found considerable variation in the susceptibility of human subjects to nitrous oxide. While some subjects were invariably unreactive to all normal stimuli when exposed to 35 per cent N₂O, others were still talkative under 40 per cent and did not lose contact with their environment until there was 45 per cent N₂O in the inspired gas. Moreover, individual subjects vary in their susceptibility from day to day in a manner which apparently depends upon whether they feel sleepy or alert. These

facts make it difficult to define a concentration of nitrous oxide at which the amnesic effects that can be revealed by our tests are easy to demonstrate. In general, we have been able to record impaired memory for recent information when the subject is breathing a concentration of N_2O some 5 to 10 per cent lower than the critical concentration required to "put him to sleep."

Our procedure in these memory tests has been as follows. While breathing mixtures of nitrous oxide in oxygen the subject was shown a number clearly written on a card. The number, chosen at random from the series 1-12 was shown to the subject for 2 sec., and an indication that the number had been recognized was obtained. At 1/2, 2, and 5 min. after exposure of each new figure, the subject was handed a piece of paper and asked to record (*a*) the number that he was last shown, (*b*) all numbers that he had been shown in their correct order, (*c*) all numerals from one to ten, in order to test his ability to write. The inspired anaesthetic concentration was increased in steps and after 5 min. of exposure to each new concentration the number was presented and the subject's memory tested. Thus, because it takes at least 5 min. for cerebral equilibration with a new N_2O mixture (5) consecutive tests of recall were necessarily separated by about 10 min.

It was apparent that there is a concentration of nitrous oxide in the inspired gas which does not prevent the subject from writing normally or from conversing intelligently with those conducting the experiment, but which does prevent him from retaining new information, of the sort that we offered, for more than 1 or 2 min. Information which could not be recalled while under the anaesthetic could also not be recalled after the subject was returned to breathing pure oxygen. Tables I and II show the results of such experiments. As a control for the experiment of Table II we have exposed the same subject when breathing air to a similar set of numbers shown under identical conditions and no errors or omissions were made.

It is worth pointing out that the errors of recall illustrated in these tables are not random. Subjects always exhibited a tendency to return to the last number that had been recalled for 5 min. Thus, in Table II under 40 per cent N_2O , the

TABLE I
EFFECT OF VARIOUS CONCENTRATIONS OF N_2O ON MEMORY AND TIME ESTIMATION IN SUBJECT 2

Percentage of N_2O in O_2 in order used	Numeral shown	Response of subject* after			Estimate of 15 sec. (sec.)
		0 5	2 (min.)	5	
10	2	2	2	2	27
20	6	6	6	6	29
25	1	1	1	1	30
30	8	8	8	8	40
35	3	3	3	3	35 5
37	4	4	4	4	45
42	5	5	(4)	(4)	∞
42	7	(4)	(—)	(—)	∞
42	9	9	9	(—)	∞
37	10	(—)	(4)	(4)	—
35	12	12	12	(10)	—

*All errors and omissions are in parentheses

TABLE II

EFFECT OF VARIOUS N₂O CONCENTRATION ON MEMORY AND TIME ESTIMATION IN SUBJECT 5

Percentage of N ₂ O in O ₂	Numeral shown	Response of subject* after			Memory of series at fifth minute						Mean estimate of 15 sec. (sec.)
		0 5	2 (min.)	5							
0	—	—	—	—	—						18 1
10	3	3	3	3	3						19 7
20	8	8	8	8	3	8					19.9
30	5	5	5	5	3	8	5				21 6
35	2	2	2	2	3	(5)	(8)	2			23.4
40	6	6	(2)	(2)	3	(5)	(8)	2	(—)		25 4
43	7	7	(2)	(2)	3	(5)	(8)	2	(—)	(—)	27 5
0	—	—	—	—	3	(5)	(8)	2	(—)	(—)	18 4

*All errors and omissions are in parentheses.

number 6 was retained for 1/2 min., but 2 min. after exposure the subject's response reverted to the number 2 exhibited under 35 per cent N₂O. The same tendency is displayed in Table I.

Note on the effects of diethyl ether. The clear-cut effect of N₂O upon learning demonstrated by Summerfield and Steinberg (2) and reported above, could be a specific property of N₂O or a property of all anaesthetic drugs. In our only experiment with diethyl ether, the subject of Table II exhibited a similar defect of learning. When his arterial blood contained 31.5 mg. of diethyl ether per 100 ml., his performance was equivalent to that when inhaling 40 per cent N₂O.

In this experiment the concentration of ether in the blood was progressively raised to 36.4 mg./100 ml. The subject had no recollection of any part of the experiment after the blood concentration reached 30 mg./100 ml., a period of 21 min. Despite this amnesia for recent events, the subject was capable during this time of directing the correct control of the anaesthetic apparatus and other prearranged experimental plans.

Notes on the general performance of subjects inhaling N₂O. Subjects inhaling a concentration of N₂O sufficient to prevent the recall of numbers which they had seen more than 1 min. earlier were able to write normally and able to converse "intelligently" with personnel conducting the experiment. Subjects who had recently learned English were still able to think and converse in this language. This sort of casual observation revealed no behavioural abnormalities. Nevertheless, abnormalities of behaviour can be revealed in subjects breathing 30 per cent N₂O (by psychological tests (6)). We were able, with the help of Dr. Brenda Milner (Clinical Psychologist, Montreal Neurological Institute), to expose some of our subjects while breathing N₂O to a few psychological tests which are listed in Table III. This table shows a comparison of the performance of the same subject when breathing air and when inhaling 40 per cent N₂O in oxygen. The figures of efficiency listed provide the ratio of the subject's score while under 40 per cent N₂O to his performance in air.

The subject of Table III proved quite incapable of performing the Wisconsin Card sorting test while under anaesthetic, although his scores were normal when he was breathing air.

TABLE III

Tests	Efficiency
Wechsler Intelligence	
Digit span	0.69
Mental arithmetic	0.50
Block design	0.57
Digit symbols	0.62
Wechsler Memory	
Immediate story recall	0.55
Visual recall	0.57
Paired associates	0.80

Effects of Nitrous Oxide on the Apparent Passage of Time

Human subjects. One of the notable features of light nitrous oxide anaesthesia is a disturbance in the subject's sense of the passage of time. The duration of the experiment invariably appeared to the subjects to be much shorter than was actually the case. Comments by the subjects in our early experiments led us to attempt a numerical estimate of the subjective passage of time.

Subjects were asked to tap an electrical key repeatedly once every 15 sec., during a control period while breathing oxygen, during the inhalation of a nitrous

FIGURE 1. Estimates of 15 sec. during a control period of O₂ inhalation, during 20 min. inhalation of 20 per cent N₂O in O₂ and during a final control period. Subject 2.

FIGURE 2. Estimates of 15 sec. during a control period of O₂ inhalation, during 10 min. inhalation of 20 per cent N₂O in O₂ and during a final control period. Subject 5.

oxide-oxygen mixture and again during a final control period. The contacts made by the key were registered on continuously moving paper. No communication was made with subject throughout the test and disturbance in the laboratory was kept to a minimum. Figures 1, 2, and 3 show the results of typical experiments on three different subjects. Directly subjects inhaled the nitrous oxide-oxygen mixture their estimates began to increase to a new and longer mean value. On returning these subjects to oxygen their time estimates rapidly reverted to the original control levels. During the first 15 min., the whole first control period of Figure 1, the subject's estimates climbed steadily so that the effect of N₂O inhalation was not clear until the subject was returned to breathing oxygen. The results of both Figures 1 and 2 indicate that the change from breathing N₂O to breathing pure oxygen produces a comparatively rapid reduction in the subject's time estimates. The increase of time estimations during the first minutes of the control period which shows in Figures 1, 2, and 3 has been observed by Waksburg (7), and this phenomenon forced us to adopt a prolonged first control period of about half an hour as is shown in the experiment of Figure 3. Figure 3, in addition to showing the effects of nitrous oxide, demonstrates the consequences of sensory disturbance. An abrupt fall in time estimates occurred when the

ESTIMATE OF 15 SECS.

FIGURE 3. Estimates of 15 sec. during a control period of O_2 inhalation during 47 min. inhalation of 30 per cent N_2O in O_2 and during a final control period. Towards the end of the period of N_2O administration the subject complained of discomfort due to the face-piece. Subject 5.

subject began to complain of discomfort from pressure of the anaesthetic mask, which made us terminate the administration of nitrous oxide.

The distortion of time estimate produced by nitrous oxide was dependent upon the concentration inhaled. Figure 4 shows a curve relating mean time estimates to anaesthetic concentration for subject 2 (of Fig. 1).

Time estimation by cats. Young cats were trained by mild punishment (see Methods) to estimate time intervals within the range 15–30 sec. Table IV shows

TABLE IV
EFFECTS OF N_2O ON CAT'S TIME SENSE

Time tested (hrs)	Breathing	Mean crossing time (sec.)	S.E.	<i>p</i>
1439–1446	Oxygen	18.5	± 2.4	< 0.01
1514–1532	35% N_2O + 65% O_2	54.2	± 7.0	—
1557–1611	Oxygen	38.9	± 5.6	0.1
1636–1643	Oxygen	19.7	± 2.3	< 0.01

NOTE: This cat was trained in air to cross the barrier between the fifteenth and the thirtieth second. The standard error of the mean crossing times is provided in column four. The fifth column gives the probability that the differences in mean crossing times from those observed under N_2O could have arisen by chance.

FIGURE 4. The relation between mean estimates of 15 sec. and concentration of inhaled N_2O in O_2 obtained in one experiment with Subject 2, exposed successively to 0, 20, 30, 10, 25, 0 per cent N_2O in O_2 . The mean time estimates are plotted together with their standard errors. Each mean was determined in the last 5 min. of a 15 min period at each concentration of N_2O tested.

the performance of one cat during an initial control period, breathing oxygen, a period of breathing 35 per cent N_2O/O_2 and two final control periods on oxygen. These tests were run consecutively with no periods of retraining between tests. Thus, during the tests the animals received no electric shocks. This way of testing is essential in order to eliminate possible effects of nitrous oxide on the animal's threshold for electrical excitation. The animal's mean estimate of time was increased approximately threefold by the administration of nitrous oxide. It will be seen that recovery was not complete 25 min. after exposure to nitrous oxide; this finding is very different from our observations on humans who recover comparatively rapidly.

On casual inspection, cats breathing 35 per cent N_2O/O_2 showed no other deviations from normal behaviour. They walked normally and moved with normal speed; they would purr and play.

DISCUSSION

The work of Summerfield and Steinberg (2), taken together with the few results that we have reported above, makes it clear that the inhalation of 30-40 per

cent of nitrous oxide in oxygen interferes with the learning of meaningless material. This finding need not imply that the same concentration of nitrous oxide would produce amnesia for all sorts of sensory experience; nor need it imply that the production of amnesia is a property of all general anaesthetics. Nevertheless, Artusio (3) has demonstrated amnesia under light ether administration. Moreover, it is well known that ethyl alcohol has similar effects. These points seem to be of sufficient practical importance to merit further investigation. It would be useful to know the lower limits of anaesthetic concentration at which those sensory experiences likely to occur during surgical operation would not be remembered; this has been done for diethyl ether by Artusio (3).

The study of any controllable procedure which interferes with learning is likely to produce information about the nature of the learning process. There is considerable evidence that both concussion and electroshock are accompanied by a variable period of retrograde amnesia. Trotter (8) defined concussion as "... a transient state due to head injury which is of instantaneous onset, manifests widespread symptoms of a purely paralytic kind, does not as such comprise any evidence of structural cerebral injury and is always followed by amnesia for the actual moment of the incident." The extent of memory defects following cranial injury has been studied by Williams and Zangwill (9) who employed psychological tests. It is generally agreed that electroshock in humans causes a variable retrograde amnesia. Janis (10) studied the nature and extent of amnesia produced by E.C.T. and commented that although amnesia was "spotty" the subjects usually exhibited most difficulty in the recall of recent events.

There is an unfortunate absence of quantitative information concerning the amnesia produced by electroshock in humans (but see Kronholm and Molander (11)). On the other hand, the results of experiments in which rats received electroshock (12, 13) have shown shock to be associated with a retrograde amnesia of some 20 min. duration. Burns (14) has pointed out that there may be a mechanism common to the events of concussion and electroshock; there is evidence that a form of Leao's (15) spreading cortical depression accompanies both conditions.

The information available about concussion and electroshock tells us little about those neurophysiological changes which accompany memory formation, but indicates that these changes, whatever their nature, are peculiarly vulnerable soon after they have occurred.

At first sight there are two possible interpretations which might be made of the observed effects of N_2O on the learning of meaningless material. One could assume that those changes produced in the central nervous system by recent learning decayed more rapidly in the presence of N_2O than they do in subjects breathing air. This interpretation would make the effects of N_2O on the central nervous system appear similar to those of concussion and electroshock. However, this assumption is not consistent with all of the available facts. Summerfield and Steinberg (2) have shown that N_2O not only reduces the rate of learning but also retards the rate of forgetting. They have pointed out that this unusual persistence of previous memories may itself be responsible for the decreased rate of learning in subjects breathing N_2O . Our own results illustrated in Tables I and II are entirely consistent with this view; in the fifth line of Table II, when the subject was expected to recall the figure "6" after 2 min., he not only failed to

recall the correct numeral but offered with confidence the numeral "2." It would be easy to interpret this observation by assuming that an abnormally persistent response of the subject to the number "2" prevented the following numbers from being learned.

One of the most remarkable effects of N_2O is the disturbance it produces in the subject's ability to estimate correctly the passage of time. The curve of Figure 4 suggests that one might usefully define "consciousness" as the reciprocal of the subjective time estimate. Whatever the mechanism by which human subjects assess the passage of time it is clear that memory forms an essential element. Unfortunately, we do not know whether amnesia, however produced, is invariably associated with disturbances in time sense. This problem would be well worth investigation; that such an investigation might prove profitable is suggested by the observation of Williams (16) who investigated patients with Korsakow's syndrome and subjects exposed to E.C.T. and concluded that "localization in time and the recall of serial order of recent events are aspects of memory particularly liable to dissolution in organic amnesic states." In the case of N_2O we have an empirical correlation between amnesia for number and disturbance of time judgment. The fact that dilute N_2O produces the same disturbance of time judgment in cats as it does in humans suggests that the action of the drug is similar in both species. This is a point of some technical importance because it provides another procedure which is known to interfere with the learning process and which can therefore be used to test potential learning mechanisms at the cellular level in experimental animals. For example, the synaptic facilitation proposed by Eccles and MacIntyre (17) as a hypothetical mechanism of learning could readily be tested for its susceptibility to N_2O .

We have not here attempted any discussion of possible mechanisms of time judgment. This problem is considered in another publication (4) where the effects of N_2O upon sensory thresholds are reported.

SUMMARY

1. Human subjects and cats breathing a weak mixture of nitrous oxide (10–40 per cent) in oxygen have been observed.
2. Human subjects breathing 30–40 per cent N_2O are not able to retain and recall new information for a period exceeding 2 or 3 min.
3. Both human subjects and cats when breathing 10–40 per cent N_2O estimate time as passing more slowly than do the same subjects breathing oxygen or air.
4. In human subjects, deviation from normal time sense increases with increasing dose of anaesthetic.

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RÉSUMÉ

Dans un travail récent, Summerfield and Steinberg (2) nous ont démontré clairement que des quantités relativement petites de protoxide d'azote dans l'air inspiré pouvaient nuire à l'établissement du souvenir de choses nouvelles. L'inhalation d'un mélange de 30% de protoxide d'azote dans de l'oxygène retarde ou diminue la capacité d'apprendre mais elle semble aussi réduire la vitesse d'oublier. Les expériences décrites dans ce travail et dans le suivant sont un sondage pour essayer de trouver comment le protoxide pourrait produire ces effets. Cela présente un grand intérêt et pour les anesthésistes qui, de plus en plus, emploient des plans d'amnésie en clinique et pour les physiologistes parce que tout procédé contrôlable qui pourrait nuire à la faculté d'apprendre pourrait bien, en définitive, apporter des renseignements sur le mécanisme de la capacité d'apprendre au niveau cellulaire. La plupart des résultats d'expériences que l'on donne plus loin illustrent un dérangement occasionné ou produit par l'inhalation de protoxide d'azote par des humains ou des chats des évaluations de périodes de temps qui s'écoulent.

Les tableaux 1 et 2 montrent les effets de diverses concentrations de protoxide d'azote sur la capacité de se souvenir de chiffres et confirment, de façon simple, le travail de Summerfield et de Steinberg. Le tableau 3 donne une vue d'ensemble de l'impuissance à subir les tests ordinaires d'intelligence chez un sujet qui respire 40% de protoxide d'azote dans de l'oxygène. Le tableau 4 montre l'effet que produit le protoxide d'azote sur l'aptitude à mesurer une période de temps chez un chat entraîné. Les schémas de 1 à 3 montrent les effets de l'inhalation de protoxide d'azote, chez trois sujets, sur l'évaluation de périodes de 15 secondes; le schéma 4 montre la relation entre diverses concentrations inhalées de protoxide d'azote et les évaluations de périodes de 15 secondes.

La courbe du schéma 4 suggère que l'on pourrait, à toute fin pratique, définir l'état de conscience comme la réciproque de l'évaluation subjective du temps qui passe. Peu importe le mécanisme par lequel les humains évaluent le temps qui passe, il est manifeste que la mémoire joue un rôle essentiel. En employant le protoxide d'azote, nous établissons une corrélation empirique entre l'amnésie de chiffres et la perturbation dans l'évaluation d'une période de temps. Le fait que le protoxide d'azote produit les mêmes perturbations chez le chat et chez l'homme en ce qui concerne l'évaluation de périodes de temps, ce fait laisse croire que l'action du médicament est la même chez les deux espèces. Les mécanismes probables de l'évaluation du temps qui passe font l'objet du travail suivant.

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