NITROUS OXIDE ANAESTHESIA INDUCED AT ATMOSPHERIC AND HYPERBARIC PRESSURES

PART I: MEASURED PHARMACOKINETIC AND EEG DATA

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SUMMARY

Anaesthesia was induced in two volunteers using 100% nitrous oxide and 92%, 87% and 80% nitrous oxide with oxygen, at atmospheric pressure; 50% nitrous oxide with oxygen at 2 atmospheres absolute (ATA); and 85% nitrous oxide with oxygen at 1.2, 1.4, 1.6 and 2 ATA. Measurements included: the duration of induction up to the subject's failure to respond to auditory stimuli (time to no response or TNR) and comparison of this with the time to a specific change observed in corresponding bifrontal electroencephalograms; pulmonary ventilation and net gas exchange, using a bag-in-box system; end-tidal concentration of nitrous oxide using an infra-red gas analyser; indirect systolic arterial pressure and e.c.g. Each subject presented characteristic patterns of ventilation, arterial pressure and pulse rate, but there were anomalies. Net uptake correlated less well than expected with the partial pressure of nitrous oxide administered, particularly with subject B for whom there was a very close correlation between TNR and time to a specific change in the e.c.g. Using different concentrations of nitrous oxide at about the same partial pressure, relative TNRs were consistent with the "concentration effect". Some clinical effects of short-term hyperbaric nitrous oxide are mentioned. Explanations for most of the anomalous results emerged from a mathematical model of the experiments which is described in Part II.
TABLE I. Apparatus used and measurements made.

<table>
<thead>
<tr>
<th>Recording apparatus</th>
<th>Associated apparatus</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kymograph</td>
<td>Krogh spirometer with bag-in-box system</td>
<td>Tidal volume and net gas exchange</td>
</tr>
<tr>
<td>Mingograf 4-channel ink-jet recorder (Elema-Schönander AB)</td>
<td>Outputs superimposed: (i) Electromanometer EMT34 (ii) Photo-electric digital pulse detector</td>
<td>Indirect systolic blood pressure</td>
</tr>
<tr>
<td>Channel 1</td>
<td></td>
<td>(Digital pulse)</td>
</tr>
<tr>
<td>Channel 2</td>
<td>Sir Howard Grubb Parsons MED1 infra-red gas analyser</td>
<td>End-expired concentration of nitrous oxide</td>
</tr>
<tr>
<td>Channel 3</td>
<td></td>
<td>Lead II electrocardiogram</td>
</tr>
<tr>
<td>Channel 4</td>
<td>Electromanometer EMT33</td>
<td>Airway pressure (used to facilitate relation of Mingograf record to spirogram)</td>
</tr>
<tr>
<td>Revox G.36 twin-channel tape recorder</td>
<td>Push button and audio-oscillator Outputs from both channels later &quot;played back&quot; on two channels of Mingograf recorder</td>
<td>Subject's response to spoken numbers</td>
</tr>
<tr>
<td>Single-channel tape recorder</td>
<td>Universal amplifier; gain at 100 microvolts cm; high frequency filter at 30 Hz; time-constant 0.3 sec; paper speed 2.5 cm/sec</td>
<td>Audiomonitor of experiment</td>
</tr>
<tr>
<td>Mingograf ink-jet recorder (Elema-Schönander AB)</td>
<td>Universal amplifier; gain at 100 microvolts cm; high frequency filter at 30 Hz; time-constant 0.3 sec; paper speed 2.5 cm/sec</td>
<td>Bi-frontal electroencephalogram (hyperbaric experiments only)</td>
</tr>
</tbody>
</table>

TABLE II. The nine conditions under which nitrous oxide was administered to two volunteers.

<table>
<thead>
<tr>
<th>Expt.</th>
<th>Partial pressure of N₂O inspired (mm Hg)</th>
<th>Ambient pressure during experiment (ATA)</th>
<th>Concentration of N₂O administered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80/1</td>
<td>573</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>87.5/1</td>
<td>626</td>
<td>1</td>
<td>87.5</td>
</tr>
<tr>
<td>92/1</td>
<td>655</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>100/1</td>
<td>715</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>50/2</td>
<td>746</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>85/1.2</td>
<td>743</td>
<td>1.2</td>
<td>85</td>
</tr>
<tr>
<td>85/1.4</td>
<td>868</td>
<td>1.4</td>
<td>85</td>
</tr>
<tr>
<td>85/1.6</td>
<td>1001</td>
<td>1.6</td>
<td>85</td>
</tr>
<tr>
<td>85/2</td>
<td>1252</td>
<td>2</td>
<td>85</td>
</tr>
</tbody>
</table>

*In referring to these experiments in the text the letter of the appropriate subject has been added, e.g., 85/2B refers to the experiment in which subject B breathed 85% N₂O at an ambient pressure of 2 ATA.

The hyperbaric experiments were carried out on consecutive days in a single working week in the order shown in table II. Subject A was always anaesthetized first and allowed to recover clinically before subject B was anaesthetized.

Pulmonary ventilation and net gas exchange.

Inspired and expired tidal volumes, and their difference (net gas exchange), were measured using two bag-in-box systems (fig. 1), one charged with air and the other charged with a mixture of nitrous oxide and oxygen (Donald and Christie, 1949). The contents were humidified to eliminate exchange of water vapour.

The subject, the spirometer, a bag* and its containing box formed a closed system. The box being rigid, the spirometer accommodated the subject's tidal change in lung capacity, and so recorded tidal volume. Assuming a constant functional residual capacity (FRC), any change in the total volume of gas in the system, as a result of net gas uptake or elimination, was reflected as a corresponding change in volume.

**TABLE III. Measured parameters.**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (years)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>FRC in sitting position (litres)</th>
<th>Sex</th>
<th>Apparatus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td>Deadspace: breathing air</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td>breating N₂O</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>33</td>
<td>1.82</td>
<td>1.78</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td>120 ml</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
<td>140 ml</td>
</tr>
</tbody>
</table>

*60-litre p.v.c. Douglas bags (their permeability to nitrous oxide being negligible in the context of the present experiments).

†18-gauge tinned sheet iron, reinforced diagonally by angle iron welded to the sides.
of end-expired position as recorded on the spirogram (fig. 2). (Observing the subjects hyperventilating while breathing 100% nitrous oxide, it seemed unlikely that the functional residual capacity (FRC) would have remained constant during that particular experiment.)

Net uptake is the difference between the uptake of nitrous oxide and oxygen on the one hand, and the elimination of nitrogen and carbon dioxide on the other. With steady ventilation, oxygen uptake can be estimated to exceed carbon dioxide excretion by about 50 ml/min in these subjects. During nitrous oxide administration, nitrogen will be excreted at a rate which may be estimated to nearly cancel this; during recovery nitrogen uptake will be added to the oxygen uptake, giving a net non-nitrous oxide uptake of about 70 ml/min (STPD).

The gas mixtures were made up in p.v.c. Douglas bags* using a calibrated 1-litre syringe. The concentration of oxygen was checked using a Servomex OA150 paramagnetic oxygen analyser (Ellis and Nunn, 1968). Sufficient gas mixture was prepared for two experiments and the bag-in-box system was recharged while subject A was recovering from the first experiment.

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*See footnote on p. 4
The subject wore a nose-clip and breathed through a double-flanged rubber mouthpiece. One flange was placed in the usual manner between gums and lips. The second flange was placed outside the lips and was secured to the face by means of adhesive tape in order to prevent leaks while the subject was unconscious. Tags were left to facilitate rapid release of the subject from the apparatus.

A three-way tap connected the mouthpiece to the breathing system (fig. 1). One position of the tap connected the subject to ambient air. The other two positions made connection with alternative bag-in-box systems, each of about 45 litres capacity and each with its own non-rebreathing valve (Hook and Tucker Ltd). The two boxes were connected to each other, to a Krogh spirometer, and to a heat exchanger through which common connection was made to both expiratory valves. Although the two boxes were interconnected, each box could be used only with its own bag, and the three-way tap could introduce only one bag at a time. The heat exchanger was a copper cylinder rilled with copper gauze which cooled expired gases to within 0.5 °C of the ambient temperature. This was checked using a thermocouple of low heat capacity.

End-expired concentration of nitrous oxide.

Expired gases were sampled continuously from a point just distal to the appropriate expiratory valve and analysed for nitrous oxide using a Grubb Parsons MED1 infra-red gas analyser (IRGA) (Hill and Stone, 1964). The sample was returned to the breathing system at a point downstream. At the sampling rate used (400 ml/min) the 90% response time was 0.7 sec. The IRGA was calibrated, at the appropriate ambient pressure, by injecting mixtures of nitrous oxide and oxygen (or air) made up in a 100-ml syringe, due correction being made for water vapour. The calibration was checked against a Servomex OA150 paramagnetic oxygen analyser. The calibration was non-linear, giving reduced discrimination at the upper end of the scale. “Overlap” response to carbon dioxide was avoided by the narrow band infra-red filter incorporated in the analyser, and in the context of the experiments the “collision broadening effect” (Bergman, Rackow and Frumin, 1958) was negligible when the ambient pressure was atmospheric. Even at 2 atmospheres absolute (ATA), 10% carbon dioxide increased the reading for 80% nitrous oxide by only 2% of full scale. Thus no correction for carbon dioxide was considered necessary at the hyperbaric pressures.

Duration of induction of anaesthesia.

The time at which the subject ceased pressing a push-button in response to prerecorded sequential spoken numbers, broadcast from a tape recorder at 3-sec intervals, was taken as an index of loss of consciousness (time to no response or TNR). The limitations of this method have been discussed by Smith and Butler (1964). Operation of the push-button actuated an audio-oscillator, the output from which was recorded on the second channel of the tape recorder. The spoken numbers and the responses were subsequently recorded again on two channels of a Mingograf recorder.

Indirect systolic arterial pressure and pulse rate.

Indirect systolic arterial pressure was recorded once every minute by superimposing the signals from an electromanometer registering cuff pressure and from a photoelectric pulse detector. The cuff was inflated to 180–200 mm Hg from a pressure reservoir and deflated to ambient pressure within 40 sec, using a time-cycled solenoid valve system and three parallel orifices which opened sequentially and provided a near-linear fall in cuff pressure. Heart rate was derived from the lead II e.c.g.

Electroencephalogram (hyperbaric experiments only).

Bi-frontal disc electrodes were fixed to the skin with adhesive discs and electrode jelly was injected under them. They were placed 3 inches from the midline towards the posterior limit of the frontal region. This position obviated the need for a head harness and shaving of the scalp, and eye movement produced less disturbance than when a more anterior frontal position was used.

Experimental procedure.

The subject relaxed in a chair for 10–15 min. Transducers were applied and calibrated. The mouthpiece was taped in position and checked for leaks and the three-way tap was turned to the “Room Air” position. Two tape recorders were switched on, one for broadcasting spoken numbers and for recording the subject’s responses, and the other to serve as a general auditory monitor. The three-way tap was turned to the “air” bag-in-box for long enough to obtain control values for pulmonary ventilation and net gas exchange, and then it was turned to the “nitrous oxide and oxygen” bag-in-box. Administration of 100% nitrous oxide was not continued beyond TNR. In the light of the e.c.g. pattern obtained during run 85/2A at the end of
nearly 2 min, 85% nitrous oxide was administered for only 1½ min in run 85/2B. In all other instances the nitrous oxide and oxygen mixtures were administered for about 2–3 min, at the discretion of the administrator. The subject was then again connected to the “air” bag-in-box, and when this was exhausted he was given ambient air to breathe.

**Precautions in the hyperbaric chamber.**

In order to reduce the chances of nitrous oxide bubbles forming in the tissues decompression was postponed until at least 1 hour after subject B’s inhalation of nitrous oxide. Instructions were given for the chamber not to be decompressed in the event of the alarm bell sounding, without first checking that this action was really required.

**Calculations.**

A computer program was prepared (K.S.) for applying corrections for gas temperature, pressure and humidity, and for the initial analysis and tabulation of results, using the Leeds University KDF9 computer.

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**RESULTS**

**Time to no response (TNR).**

The relationship between TNR and the partial pressure at which nitrous oxide was administered is shown in figure 3. The general trend was for induction time to be shorter as the partial pressure of nitrous oxide was increased; there is, however, an appreciable scatter of these results and there are anomalies.

**Electroencephalography.**

The salient features of the encephalograms are described in table IV and illustrated in figure 4. The first recognizable change in the electroencephalogram was the appearance of runs of continuous slow wave activity of 20–30 microvolt amplitude. With subject B these had a frequency of 6–7 Hz and for each hyperbaric experiment the time at which they first persisted for at least 1.5 sec (fig. 4) was noted. These times of specific change in e.e.g. pattern were assessed independently of TNR, with which there was subsequently found to be excellent correlation (fig. 5) (Smith, 1971). Due to technical difficulties a complete set of comparable records was not obtained with subject A.

**Indirect systolic arterial pressure and pulse rate.**

The measurements of indirect arterial systolic pressure and pulse rate for each experiment are superimposed in figure 6, results obtained during hypoxic experiments being shown separately. With subject A there was no consistent change in arterial
TABLE IV. Salient e.e.g. activity recorded at ambient pressure of 2 ATA.

<table>
<thead>
<tr>
<th>Subject A</th>
<th>Subject B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slow: Diminishing amplitude</td>
</tr>
<tr>
<td>Breathing N₂O at TNR</td>
<td>Slow: Amplitude increased to 20–30 microvolts (50% and 85% N₂O)</td>
</tr>
<tr>
<td>Deepening anaesthesia</td>
<td>Slow: 3–4 Hz 20–30 microvolts with runs of increased amplitude up to 100 microvolts, the duration of these increasing as anaesthesia deepened (85% N₂O)</td>
</tr>
<tr>
<td>Deeper anaesthesia</td>
<td>Runs of high amplitude slow waves lengthened, merging into a complex stage in which continuous slow waves 3–5 Hz varied haphazardly in amplitude between 30–250 microvolts (85% N₂O breathed for 117 sec; TNR at 64 sec)</td>
</tr>
</tbody>
</table>

FIG. 4. Above: Typical e.e.g. records at ambient pressure 2 ATA. (i) and (ii) Breathing air. (iii)-(vi) Breathing 85% nitrous oxide. (i) Fast wave activity. (ii) Slow waves. (iii) At time of no response. (iv) Short run of rhythmical activity. (v) Long run of rhythmical activity. (vi) Deeper anaesthesia showing complex stage in subject A. Below: Slow wave index: 6–7 Hertz; 20–30 microvolts amplitude; rhythmic continuous activity of more than 1½ sec duration.

FIG. 5. Time to no response and time to specific change in e.e.g. for subject B.

pressure or pulse rate, except that there was a slight increase in pressure from the start of the control period breathing air in the hypoxic experiments. In experiment 85/1.4A there was retching, pallor and sweating, which was preceded by tachycardia (cf. Smith and Butler, 1964, fig. 2, experiment 9; subject B of that series was subject A of the present series). With subject B of the present series there was a consistent reduction in systolic pressure during the induction of anaesthesia, with a return to pre-induction value during recovery. His pre-induction pulse rates tended to be greater before the hypoxic
anaesthetics than before the non-hypoxic anaesthetics.

Pulmonary ventilation and net gas exchange.

The patterns of ventilation for each subject are superimposed in figure 7, results obtained during hypoxic experiments being shown separately. The net uptake is plotted against inspired partial pressure of nitrous oxide in figure 8.

In the non-hypoxic experiments subject A had a fairly consistent expired minute volume initially while breathing air, and this increased consistently during the first minute of breathing nitrous oxide, returning to the control value in the recovery period in most instances. Subject B was initially more variable in his minute volume, which decreased to a consistent value after breathing nitrous oxide for about 1 min (regardless of the concentration or the partial pressure at which nitrous oxide was administered) and then tended to increase, although there were anomalies.

In the hypoxic experiments the minute volume increased steeply with both subjects during the administration of 100% nitrous oxide. During the administration of 92% and 87.5% nitrous oxide a moderate increase in minute volume was seen with subject A.

With subject A the net uptake increased with the partial pressure of nitrous oxide, although there is appreciable scatter of the results (fig. 8). This relationship is less convincing with subject B.

Observations during hyperbaric experiments.

The total net uptake at the end of the inhalation of nitrous oxide and oxygen (155 sec) in experiment 50/2A was 2.7 litres STPD, and after inhaling nitrous oxide and oxygen (114 sec) in experiment 85/1.6A it was 2.9 litres STPD. Although the total "dose" of nitrous oxide was almost the same in these two experiments, it is noteworthy that recovery of normal faculties after the former was quick, whereas it was markedly sluggish after the latter, the

FIG. 8. Net uptake in the first minute of inhaling nitrous oxide, against the inspired partial pressure of nitrous oxide. Squares indicate hyperbaric experiments. Solid circles indicate 20% oxygen in the anaesthetic mixture and open circles indicate less than 20% oxygen. With both subjects the net uptake in the first minute was less in experiment 50/2 than in experiment 85/1.2. The circle for experiment 100/1B represents the uptake at the end of induction which lasted for only 50 sec.
subject still showing signs of inebriation at least 45 min later.

Salivation appeared to increase with the partial pressure of nitrous oxide administered, although with subject A this may have been related to nausea during recovery.

Both subjects commented upon the increased pungency of nitrous oxide, faintly reminiscent of ether, during the hyperbaric experiments.

**DISCUSSION**

**Time to no response (TNR).**

The validity of the method used for comparing induction times is supported by the close correlation between TNR and the independently determined time of specific change in the e.g. in subject B.

With both subjects the TNR was longer with experiment 50/2 than with experiment 85/1.2 although in each case the partial pressure of nitrous oxide inspired was about equal to normal atmospheric pressure. This appears to be a unique demonstration of the “concentration effect” (Eger, 1963). With both experiments 50/2 and 85/1.2 the induction times were longer than with experiment 100/1. The effects of hypoxia and hyperventilation would have been superimposed on the “concentration effect” in experiment 100/1.

Although there were no previous experiments with subject B for comparison, the TNR for subject A while breathing 80% nitrous oxide (experiment 80/1A) was longer than in similar experiments carried out four years previously (Smith and Butler, 1964). Cross-checking of all available data has produced no convincing explanation for this.

**Net gas exchange and FRC.**

It was appreciated that measurement of net gas exchange using a bag-in-box system requires that the FRC remains constant (Smith, 1967). From a comparison of the measured with the theoretical results, however, it appears (see Part II) that there was an appreciable consistent reduction in FRC during the induction of anaesthesia in subject B. This was not anticipated. It implies that a more precise comparison of measured with theoretical results would require simultaneous measurement of net gas exchange and change in FRC. This is possible using a whole-body plethysmograph (fig. 9), although it is inadvisable to proceed with the induction of anaesthesia beyond TNR (Smith, Mapleson and Hargreaves, work in progress).

The reason for the lack of correlation between the net uptake in the first minute and the partial pressure of nitrous oxide with subject B is explained in Part II.

**Arterial systolic pressure and pulse rate.**

The two subjects presented different patterns of cardiovascular response to the induction of nitrous oxide anaesthesia. This may have been partly the result of their different ages and emotional response. Subject A was a more experienced experimental subject. The relatively greater pulse rates in subject B before the hypoxic induction of anaesthesia, and also before the first non-hypoxic experiment (80/1), probably reflect apprehension.

**Pulmonary ventilation.**

The two subjects also presented distinctive patterns of ventilatory response. Both were unfamiliar with the hyperbaric environment and they were aware of the possible implications of breathing hypoxic mixtures, albeit for very short periods, so respiration may have been influenced by psychological factors. Furthermore, because the nitrous oxide and oxygen mixtures were breathed for only brief periods, equilibrium was never approached. Therefore, no conclusions can be drawn from these experiments about the pharmacological effect of nitrous oxide upon respiration.

For reasons given in Part II, it is thought that there was some valve incompetence while subject B was breathing nitrous oxide and oxygen, particu-
larly during experiment 50/2B in which ventilation increased steadily after the first minute of breathing nitrous oxide. There are two possible explanations for rebreathing occurring with subject B and not subject A. Firstly, subject B always followed subject A so that excess moisture may have collected on the valves before the beginning of the second experiment of each day. Second, the breathing pattern of subject B was slower (fig. 2) and potentially more conducive to valve incompetence. Positive opening and closure of the valves are more likely with the breathing patterns of subject A. It would have been a useful precaution to use pneumotachography to monitor valve competence.

**Recovery from anaesthesia.**

The prolonged recovery period following experiment 85/1.6A compared with the brisk recovery following experiment 50/2A (despite the total net uptake at the end of each experiment being almost the same) is presumably related in some way to the higher partial pressure of nitrous oxide in 85/1.6A. It suggests that while breathing the higher partial pressure, the tension of nitrous oxide in at least a part of the brain, exceeded a threshold value beyond which recovery is prolonged.

**Acknowledgements**

The experiments carried out in the hyperbaric chamber in 1968 were made possible by the generous hospitality of the Departments of Surgery and Anaesthesia, the Western Infirmary, University of Glasgow, with the cooperation of the Department of Clinical Physics of the Western Regional Hospital Board, Glasgow. Measurements of the FRC of subject A were kindly made by the Department of Anaesthesia, the Western Infirmary, Glasgow, and the Respiratory Function Unit at the Leeds General Infirmary.

**References**


