NITROUS OXIDE HYPARGESIA IN TRAINED SUBJECTS

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"On the day when the inflammation was most troublesome, I breathed three large doses of nitrous oxide. The pain always diminished after the first four or five inspirations; the thrilling came on as usual, and uneasiness was for a few moments swallowed up in pleasure. As the former state of mind however returned, the state of organ returned with it..." These words were written by Humphrey Davy in 1800.1

It is generally accepted that a condition of hypoalgesia exists in the "twilight" zone between consciousness and unconsciousness when general anesthetics are administered. The agent most commonly used to produce the state of diminished consciousness is nitrous oxide. This gas has widespread use in obstetrics, dentistry, and general surgery because of the analgesic properties ascribed to it.

The purpose of these experiments was to study the subject's thresholds for electrical stimuli applied to filled teeth during the inhalation of nitrous oxide in concentrations up to 50 per cent, and to evaluate the factor of learning that might occur as a result of repeated experiences.

METHOD

A total of 9 adult males were used for these tests. One had had nitrous oxide several years before for the extraction of a tooth. The others were naive subjects.

The subjects reclined on a stretcher in a quiet, dimly-lit room. A filled tooth was selected, usually an upper premolar, and a small wire electrode was cemented in contact with the amalgam or gold. An indifferent electrode was secured to the right hand. The left hand was in contact with a signal key which lit a small lamp above the instrument panel in the adjoining room. Standardized instructions were given each subject. He was asked to signal by pressing the key when he felt a sensation in his tooth, and to continue to hold the key down as long as he felt it. The subjects for the tests on the just-tolerable-pain thresholds were, in addition, asked to signal by rapidly pressing the key when the sensation became as intense as they wished to experience.

A few stimuli were administered to acquaint the subject with the sensation he would feel in the tooth. The intensity of the 5 per second, 1 msec. positive rectangular pulses was gradually increased from zero to the level at which the subject pressed the key, increased somewhat above this point, and gradually decreased to a level below where the subject released the key. The voltage developed across a resistance in series with the subject was read on an oscilloscope calibrated in milliamperes. The absolute threshold was determined by the mean of these "ascending" and "descending" intensities. The just-tolerable-pain threshold was measured simultaneously with the absolute threshold in some subjects. For these subjects the intensity was gradually increased above the level at which the key was held down until the subject rapidly pressed the key. The intensity was then decreased slowly until the subject released the key. The just-tolerable-pain threshold was that intensity at which the subject rapidly pressed the key.

The initial threshold was established with the subject breathing room air through an anesthetic mask in contact with the face. Results are expressed as per cent changes from this initial threshold. Immediately following this pretest, nitrous oxide-oxygen mixtures were delivered to the subject from a McKesson anesthesia machine which had been calibrated to deliver accurate percentages at the 25, 30, 40, and 50 per cent concentrations of nitrous oxide. A threshold determination was made every 30 seconds during the 5 minutes the gas was administered. Care was taken to vary the rate of change of stimulus intensity during these determinations so that the subject could not...
in the control run, there is no evidence that the threshold increases in these runs are significant.

The 40 per cent run showed a rapid increase reaching 140 per cent and a decrease which did not quite return to the initial level by the end of the 2½ minute recovery period. A sign test applied to the data of five subjects who were in both 25 and 40 per cent runs shows that during the last minute of gas inhalation the threshold on the 40 per cent run was significantly increased ($p < .05$).

Figure 2 shows threshold changes occurring in the group of 6 subjects tested at least two different times at 40 per cent nitrous oxide.

The first run for these subjects showed large elevations in thresholds starting 2½ minutes after the onset of gas administration. The maximum elevation of 117 per cent occurred after 4½ minutes of the gas. The lower curve represents the performance of these subjects after they had experienced three or four five-minute runs while under 40 per cent nitrous oxide. The figure shows these few training trials reduced the apparent effect of nitrous oxide on threshold. A sign test on the threshold at 4½ minutes indicates that the decrease after training is significant ($p < .05$).

Figure 3 follows two different thresholds during 50 per cent gas administration and recovery on 4 subjects who had undergone threshold determinations under nitrous oxide previously. The absolute threshold indicated by the solid line showed a small gradual increase until 4½ minutes after the onset of gas when the threshold increased abruptly. At this

![Diagram](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931660/)

**Fig. 1.** Median changes in absolute threshold of naive subjects during inhalation of nitrous oxide, with control.

**Fig. 2.** Comparison of absolute thresholds before and after training, using 40 per cent nitrous oxide-oxygen.
point two of the four subjects were apparently unconscious in that they did not respond to stimuli five times the initial value. After a half minute of room air the median absolute threshold showed only a slight elevation and at the end of the recovery period this threshold had returned to its initial level.

The broken line in figure 3 represents the avoidance point or threshold of just-tolerable pain taken on the same subjects. This avoidance point has been expressed as a per cent of an initial avoidance point established in the pretest. Relative to the absolute threshold, this avoidance point was from 10 to 35 per cent higher. The figure shows the two thresholds behaved identically when these subjects inhaled 50 per cent nitrous oxide. The thresholds increased and decreased together with no indication that the painful quality of the stimulus disappeared without a concomitant change in absolute threshold.

**DISCUSSION**

The sensations experienced during the inhalation of nitrous oxide and oxygen have been described numbers of times. It is not a pleasant experience to all. In a conventional induction during inhalation anesthesia, consciousness is lost rapidly, but in the present experiment the first stage was prolonged with no deliberate intent to produce unconsciousness. The individual experiencing the effects of the gas was usually aware of a terrific pounding in his ears, far faster in tempo than the heartbeat. The sound seemed to engulf everything, although all sounds seemed exaggerated in volume. If he could disregard the pounding, he was aware of a delightful warmth sweeping over his body.

He experienced a flight of ideas and thoughts that he had a compelling urge to transmit, but which were usually forgotten when full consciousness returned. Sometimes he had difficulty in restraining himself either physically or vocally, but most test subjects succeeded. The stimulus to the tooth broke into the delirium and alerted the subject into signalling with the key. He was sure that he was far from accurate in his response to the stimulus, and often times frantically pressed the key as though afraid the intensity would be increased before he could signal.

The difficulties of establishing a constant threshold of experimental pain in subjective testing is well documented. In the present experiment we have used the absolute threshold (barely-perceptible sensation) in preference to the pain threshold (barely-perceptible pain), or avoidance threshold (just-tolerable pain) studied by other investigators. The parallel rise and fall of the absolute and avoidance thresholds (fig. 3) suggests that measurements of the tooth absolute threshold may give as valid an indication of pain sensitivity as measurements of the pain or avoidance thresholds themselves. Inasmuch as the stimulus for the absolute threshold was less likely to result in local tissue changes in the tooth, and avoided the various psychological factors associated with the interpretation of pain, it was used in our testing. The results of our experiments with naive subjects are in close agreement with those of Persson.

An unexpected result of the testing was the influence of learning on the effects of nitrous oxide. With one exception, no more than five test runs were required before the subject learned to discriminate the stimulus from the general state of mental confusion resulting from the inhalation of the gas. This variable has not been taken into account in some of the earlier studies. The factor of learning, together with the close correlation between the absolute threshold and the avoidance threshold lead one to conclude that an interpretation of the term "nitrous oxide analgesia" must be elastic enough to include the part played by confusion. One cannot assume from these test that nitrous oxide produces a state of analgesia comparable to that observed in patients to whom
a moderate but effective dose of morphine has been administered.

SUMMARY

A study has been made of the effects of various concentrations of nitrous oxide upon the thresholds for electrical stimuli applied to filled teeth. Nine subjects without previous experience with nitrous oxide were tested. 25, 30, 40, and 50 per cent concentrations of gas were used. The absolute threshold was the point at which the stimulus was just felt, and the avoidance threshold was at an intensity where just-tolerable-pain was noted. The two thresholds were found to run parallel courses with no indication that the painful quality of the stimulus disappears without a concomitant change in the absolute threshold. It was also found that after several periods of testing the subject became more experienced with the confusion state resulting from the inhalation of nitrous oxide and his absolute threshold during inhalation approached that of the control runs.

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REFERENCES