THE INFLUENCE OF PARTIAL PRESSURE OF NITROUS OXIDE ON THE DEPTH OF ANESTHESIA AND THE ELECTRO-ENCEPHALOGRAM IN MAN *

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SINCE Andrews (1), in 1868, first advocated the use of mixtures of nitrous oxide and oxygen in anesthesia, anesthesiologists and physiologists have been concerned with the relationship of hypoxia to nitrous oxide anesthesia. Probably the first critical study of this question was made on dogs by Bert (2) in 1878. He found that he could administer nitrous oxide and oxygen, five parts of the former to one part of the latter, in a specially constructed chamber at 1.2 atmospheres of pressure and produce anesthesia without clinical signs of hypoxia. Later investigators have questioned Bert's conclusions. Some of these authors leave the reader with the impression that hypoxemia is essential to the production of anesthesia with nitrous oxide. Leake and Hertzman (3) reported as follows: "Under nitrous oxide and oxygen it is impossible to maintain satisfactory anesthesia without some degree of anoxemia." Greene and Currey (4) in a report made in 1925 on a series of well-controlled experiments on dogs give the reader the same impression. Neither of these investigators, however, dealt with anesthesia under increased atmospheric pressure. In 1927, Brown, Lucas, and Henderson (5), working with cats and rabbits, experimented with mixtures of nitrous oxide and oxygen in which partial pressures of nitrous oxide of as much as 1,320 mm. of mercury were used, and concluded as follows: "Surgical anesthesia cannot be produced with oxygen-nitrous oxide mixtures under pressures up to 2 atmospheres if the partial pressure of the oxygen is equal to that in the atmosphere, namely 156 mm."

Since we were unable to justify or explain the impressions left by such papers as those mentioned in the light of modern understanding of respiratory physiology, it was our desire to answer the question, "Can nitrous oxide be administered to a human being in a manner that will exclude hypoxemia and produce a level of anesthesia comparable

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to that required for ordinary surgical procedures?" We use the term "hypoxemia" advisedly and include in it all forms of anoxia except histotoxic, as defined by Barcroft (6).

The differences in experimental results of the authors quoted may be partially explained by the difficulty in estimating both hypoxemia and depth of anesthesia in animals. In addition it is uncertain to what extent conclusions drawn from the less highly organized nervous system of lower mammals can be applied directly to the problems of anesthesia in man. It was considered essential for a satisfactory solution of the problem, therefore, that (1) studies should be made on normal persons, (2) an accurate method should be used for estimating the depth of anesthesia and degree of hypoxemia and (3) electrical potentials arising from the brain should be recorded to give objective information concerning the narcotic effect of the anesthetic mixtures.

Preliminary studies were performed by the authors on themselves. The effects of a mixture, 25 per cent nitrous oxide and 75 per cent oxygen at 1 atmosphere of pressure and at 2 atmospheres of pressure, were compared. We found that symptoms of euphoria and confusion were greatly increased under the higher pressure.

METHODS

Observations were made on 5 healthy persons, aged from 20 to 35 years who agreed to the study. No medication was given before the study and a full meal was not taken less than two hours before.

Apparatus.—The pressure chamber used was a small tank large enough to contain a person in the supine position, an anesthetist, an assistant and essential equipment. The tank could be maintained accurately at any desired positive pressure for long periods. There was a telephonic communication between the tank, the control panel and the electro-encephalographic recording room.

To avoid the use of an anesthesia machine or any rebreathing device which would involve dilution of the anesthetic mixture with nitrogen, a direct flow mechanism was constructed. From oxygen and nitrous oxide cylinders situated outside the pressure chamber, the two gases were piped separately into the chamber at a gauge pressure of about 100 pounds (45.4 kg.) per square inch. The gas outlets within the chamber were connected by pressure tubing to two demand flow valves of aviation type. The valves operated at a line pressure of more than 75 pounds (34 kg.) per square inch. They allowed a free flow of gas on inspiration but were automatically shut off during expiration. The outlets from the demand flow valves were connected to corrugated rubber tubing which had a minimal inside diameter of ¾ inch (1.9 cm.). The two gases were mixed through a Y connector leading to a similar corrugated tube which was connected to an air force demand mask (model A-14). This mask had standard inspiratory and expiratory valves of the American Air Forces. The percentage constituency of the gas mixture delivered to the subject was controlled by pinch clamps which could be made to constrict either the nitrous oxide or oxygen tube between the demand flow valve and the Y connector. The gas mixture was sampled by suction from a T connection placed close to the mask through a Pauling oxygen meter (model D). This meter has a scale reading from 0 to 100 per cent oxygen and is accurate within ± 2 per cent.

Oximeter.—In four of the studies oxygen saturation of arterial blood in the ear was evaluated continuously by means of a compensating Millikan oximeter. This instrument had been calibrated by blood gas analysis and had been found to give accurate indications of change in oxygen saturation, though absolute values were subject to errors from individual variations in thickness of the ear. Since a normal resting arterial saturation can be assumed in our subjects, the changes in the saturation were of importance.

Electro-encephalograph.—A two channel electro-encephalograph was available for observations on cortical potentials. Since previous work had shown that the changes in potentials with anesthesia usually occur symmetrically in the two hemispheres, observations were confined to the left hemisphere in all instances. This ensured the most economical use of the two channels available. Frontal electrodes were avoided to reduce artefacts that might have arisen from eye movement or manipulation of the mask during induction of anesthesia. Electrodes of solder type with contact jelly were placed 3 inches (7.6 cm.) apart and 1½ inches (3.8 cm.) from the midline beginning ½ inch (1.3 cm.) above the inion. Bipolar connections were made through screened leads to the input of a Grass two channel inkwriting oscillograph of standard design (time constant, 0.25 second) which was housed 45 feet (1371.6 cm.) from the pressure chamber. At the high frequency position (F. 3) used in these studies the long screened input lead did not affect the frequency response appreciably. A careful watch was kept for the possibility of artefacts arising from eye and head movements, or hyperventilation during the induction of anesthesia.

Procedure.—The subject, anesthetist, assistant and equipment were in the pressure chamber. After the equipment was adjusted control runs were made with the oximeter and the electro-encephalograph at the existing barometric pressure with the door of the chamber open. Then, in the first four studies, a mixture of approximately 50 per cent nitrous oxide and 50 per cent oxygen was administered to the subject by the direct flow technic, previously described, for a period of five minutes at the existing barometric pressure, usually about 730 mm. of mercury (partial pressure of oxygen 365 mm. and of nitrous oxide 365 mm.). The subject was allowed to recover for a period of about ten minutes; the chamber door then was closed and the atmospheric pressure in the chamber was increased to 1520 cc. of mercury. The time required for this change in atmospheric pressure was about ten minutes. After another control run with the oximeter and the electro-encephalograph, the same gas mixture (50 per cent oxygen, 50 per cent nitrous oxide) under this increased pressure was again administered in the same way for a period varying between five and fifteen minutes. The partial pressures now being respired by the subject were 760 mm. of oxygen and 760 mm. of nitrous oxide. To control the possibility that the deeper anesthesia produced by nitrous oxide at 2 atmospheres (1520 mm.) of pressure was partly the result of the residual anesthetic effect from the previous administration at 1 atmosphere, the sequence of studies was reversed in one instance. During all of these studies the clinical observations of the experienced anesthetist conducting the anesthesia were recorded. Checks were made on the various reflex phenomena of deepening anesthesia, and the anesthetist's own estimate of the stage and plane of anesthesia in the terms of Guedel's (7) classification was recorded.

RESULTS

The results of studies on the 5 different persons (subjects 1 to 5 are presented in figures 1 to 5. Short segments of the electro-encephalographic tracing from the left parieto-occipital area have been reproduced in each figure to indicate the amplitude and frequency of the alpha and delta waves at the time indicated by the arrow.

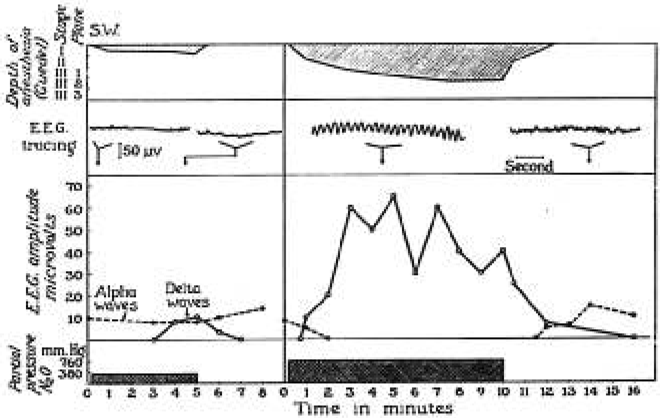

FIG. 1. Anesthetic and electro-encephalographic changes occurring in subject 1 during inhalation of a mixture of 50 per cent nitrous oxide and 50 per cent oxygen at about 1 and 2 atmospheres of pressure. The usual barometric pressure of about 730 mm. of mercury was employed instead of exactly 1 atmosphere. The partial pressure of nitrous oxide was then 365 mm. of mercury.

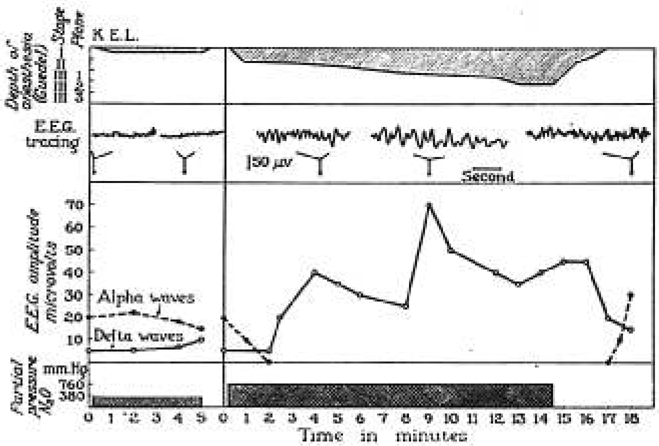

FIG. 2. Anesthetic and electro-encephalographic changes occurring in subject 2 during inhalation of mixture of 50 per cent nitrous oxide and 50 per cent oxygen at about 1 and 2 atmospheres of pressure.

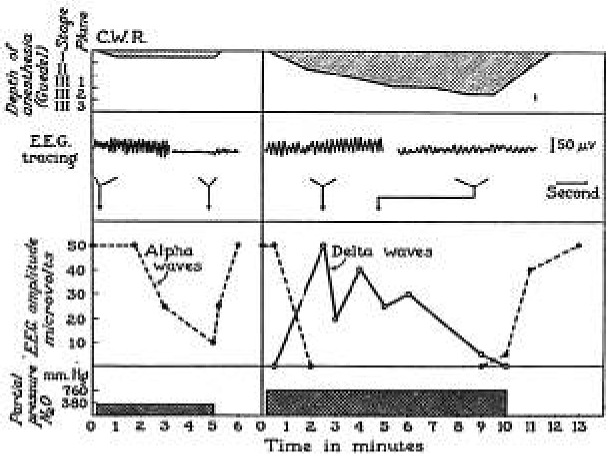

FIG. 3. Anesthetic and electro-encephalographic changes occurring in subject 3 during inhalation of mixture of 50 per cent nitrous oxide and 50 per cent oxygen at about 1 and 2 atmospheres of pressure.

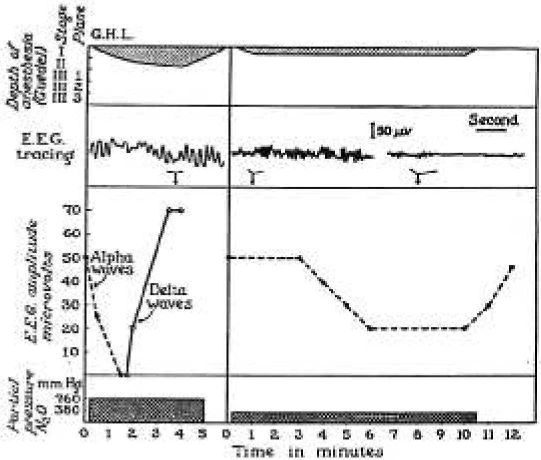

FIG. 4. Anesthetic and electro-encephalographic changes occurring in subject 4 during inhalation of mixture of 50 per cent nitrous oxide and 50 per cent oxygen at about 1 and 2 atmospheres of pressure.

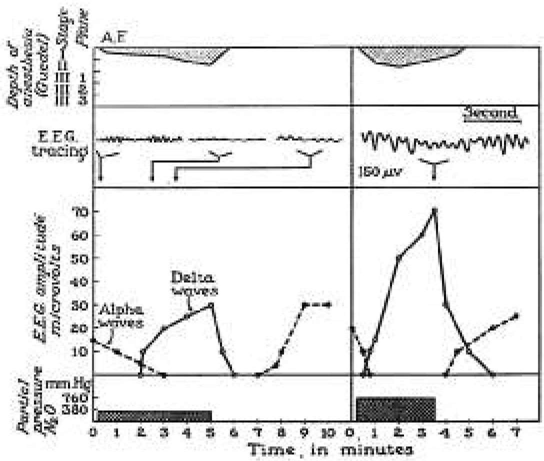

FIG. 5. Anesthetic and electro-encephalographic changes occurring in subject 5 during inhalation of mixture of 50 per cent nitrous oxide and 50 per cent oxygen at about 1 and 2 atmospheres of pressure.

Oximetric Readings.—The oxygen saturation of arterial blood did not fall more than 8 per cent during the four studies in which readings were taken and a similar range may be assumed in the fifth which was performed under conditions similar to the other four. We are unable to explain this decrease in oxygen saturation but our previous experience indicates that it does not represent a significant degree of hypoxemia.

Anesthesia.—When nitrous oxide was administered at a partial pressure of 365 mm. of mercury (partial pressure of nitrous oxide was 50 per cent of the barometric pressure of 730 mm. of mercury) for five minutes, the depth of anesthesia as judged by clinical estimate never went beyond the first stage (Guedel) in 4 persons studied (figs. 1 to 4). The fifth (fig. 5) became unconscious but still responded to painful stimuli. By contrast, administration of nitrous oxide at a partial pressure of 760 mm. of mercury (50 per cent of the barometric pressure of 1520 mm.) invariably resulted in loss of consciousness within two minutes, the excitement stage being short. At the end of the five-minute period of administration, a plane of surgical anesthesia (plane 1 or 2 of stage III) was reached in all subjects, this finding illustrates the profoundly greater effect of high partial pressure of nitrous oxide even in the presence of 760 mm. partial pressure of oxygen. The clinical findings were substantiated by the changes in cortical activity. Recovery from the anesthesia was prompt and occurred within one to two and a half minutes from the time the mask was removed from the face.

Electro-encephlograms.—While there were considerable individual differences in the resting electro-encephalograms of the 5 persons, these differences tended to be ironed out under the influence of nitrous oxide and remarkably similar patterns of activity were seen in all instances.

The first effect of nitrous oxide anesthesia was noted during stage I anesthesia (Guedel). A gradual and progressive diminution in the amplitude of the alpha waves occurred without an appreciable change in the frequency. Before the alpha rhythm was entirely eliminated it was usual for random delta waves with a frequency of between 4 and 6 cycles per second to appear in the motor, parietal and occipital regions. These were of low potential at first but gradually increased in amplitude and persistence; eventually a continuous rhythm developed. The final disappearance of the alpha rhythm corresponded closely with the clinical change from consciousness to unconsciousness (stage I to II). Furthermore, with the one exception previously mentioned (subject 5, fig. 5) continuous delta rhythms of amplitude greater than 10 microvolts were only found in the deeper stages of anesthesia produced by nitrous oxide at high partial pressure.

Once a continuous delta rhythm had been established, it increased in amplitude with deepening anesthesia usually reaching 40 to 70 microvolts. Thereafter large fluctuations in amplitude were frequently noted though no corresponding changes in the depth of anesthesia could be detected by the methods available. In addition there was a tendency for the amplitude to fall and the frequency to rise toward the end of an anesthetic period.

During recovery, return of consciousness and correct orientation were closely related to the reappearance of the alpha rhythm. Intermittent delta waves of diminishing amplitude usually persisted for fifteen to thirty minutes after full consciousness had been regained.

COMMENT

Anesthesia.—We believe that the evidence presented in this paper gives strong support to the following two contentions: 1. The anesthesia, resulting from the administration of nitrous oxide, is not dependent on a coexistent state of hypoxemia and that successful anesthesia with nitrous oxide is possible in the presence of normal oxygen saturation of arterial blood. Whether nitrous oxide acts within the cell to interfere with consumption of oxygen either by depriving the cell of access to a normal supply of oxygen or by rendering the oxygen needs of the cell below normal levels remains to be answered by other investigations. Hence it becomes impossible for us to state that anoxia, in the strictest sense of the term, need not always accompany nitrous oxide anesthesia. 2. The depth of anesthesia produced by nitrous oxide in the presence of an excess of oxygen is directly proportional to the partial pressure of the anesthetic gas.

Serious consideration should be given to Bert's seventy-year-old recommendation that means be provided for the administration of mixtures of nitrous oxide and oxygen at increased barometric pressures. In this manner the field of usefulness of this almost perfect anesthetic agent might be extended to many surgical problems now inaccessible to it.

Electro-encephalography.—The changes in the electro-encephalogram accompanying the early stages of nitrous oxide anesthesia have been described previously by Van der Molen (8). Although anoxia may have been present in his cases, the findings were in general similar to ours.

The question as to what extent the changes in potential result from the decrease in carbon dioxide which may accompany the administration of an anesthetic is pertinent both to our own studies and those of Van der Molen. However, the absence of any notable correlation between the degree of ventilation and the amplitude of the delta rhythm in our studies suggests that this is not a significant factor in producing the electro-encephalographic changes.

A question of considerable interest to anesthetists is whether or not the electro-encephalogram provides a clinically useful index to the depth of nitrous oxide anesthesia. While the data presented are insufficient to answer the question satisfactorily, there are ample indications of a general correlation between the depth of anesthesia and the serial changes in the electro-encephlogram which have been described.

SUMMARY

Anesthetic and electro-encephalographic effects of a mixture of 50 per cent nitrous oxide and 50 per cent oxygen administered at ground level (barometric pressure of 730 mm.) and at a barometric pressure of 1520 mm. of mercury have been compared. At ground level mild excitement and confusion usually occurred. This was accompanied by a diminution in the amplitude of the alpha rhythm.

At barometic pressure of 1520 mm. of mercury consciousness was lost rapidly and in most persons observed surgical anesthesia resulted. In the electro-encephalogram the alpha rhythm was replaced by a high voltage delta rhythm of 4 to 6 cycles per second.

The production of surgical anesthesia was not accompanied by significant alteration in the oxygen saturation of arterial blood.

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Panel: Fire and Explosion Hazards.
Moderator, R. L. Patterson, M.D., Pittsburgh, Pa.
Precautions When Using Flammable Agents in the Operating Room.
Sidney Katz, M.D., Cleveland, Ohio.
Grounding Devices in the Control of Static.
Nicholas Depiero, M.D., Cleveland, Ohio.
Equipment in the Operating Room.
L. E. Larrick, M.D., Cincinnati, Ohio.

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