The Anesthetic Properties of Xenon in Animals and Human Beings, with Additional Observations on Krypton[1]

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In 1946 Lawrence *et al.* (*1*) reported the effects on mice of the inhalation of xenon-oxygen mixtures. Their observations led them to believe that the inert gas possessed narcotic properties. In addition, one of the observers reported "dizziness" on the inhalation of a 50–50 mixture of krypton and oxygen. They advanced the hypothesis that the effects observed were associated with the high fat solubility of the gases and their high oil-water ratio, and were consistent with the Meyer-Overton hypothesis. In an extensive review of the literature they report the solubility of krypton as a Bunsen absorption coefficient of 0.43 in oil at 37° C and of 0.045 in water at 37° C with an oil-water ratio of 9.6. Xenon is reported to have a Bunsen coefficient of 1.7 in oil at 37° C and 0.085 in water at 37° C with an oil-water ratio of 20.

In 1948 Lazarev (*2*) reported observations on the effect of krypton and xenon on small mice, an adult mouse, and cockroaches, which led him to believe that krypton was essentially ineffective but that xenon demonstrated conclusive narcotic properties.

Butler, in a review of the general theories of anesthesia (*3*), reported on these observations with the inert gases and stated that the evidence for anesthetic effect was inconclusive. He further stated that, "If the inert gases can be considered true anesthetics, the action of these spherically symmetrical atoms without any permanent dipoles furnishes the most conclusive demonstration that anesthesia need not depend on the effect of any specific structural grouping."

The observations incident to the experiments reported in this article support Butler's contention that the evidence for narcotic effect of the inert gases in animals is inconclusive. The evidence is much more conclusive, however, with respect to the observations on human beings.

Early in 1950, a supply of krypton 95% and xenon 5% was made available, and an 80% mixture of this gas with oxygen was given to mice, rats, and rabbits in an attempt to determine its effectiveness as a narcotic. The mice and rats were placed in a cylinder through which the mixture was moved in a circuit. Oxygen was added to compensate for that used in the metabolism of the animals, and CO_2 was removed with soda lime placed in the circuit. Each group of animals was given an 80% mixture of nitrous oxide with oxygen in the same manner. Approximately 10 mice in groups of two, and 5 rats, were used in the experiments. They exhibited no unequivocal evidences of narcosis with either the nitrous oxide or krypton mixtures. The animals were then given subhypnotic doses of Nembutal, and the experiments were repeated with no significantly different results.

In a somewhat different system, which made provision for circuit breathing, addition of oxygen, and elimination of CO_2, 12 rabbits were given inhalations of either 80% krypton with oxygen or 80% nitrous oxide with oxygen. After exposures of 15 min to each gas mixture, no unequivocal signs of narcosis could be demonstrated. The rabbits also were given subhypnotic doses of Nembutal and the inhalations repeated with no significantly different results.

Three human beings inhaled from a closed system (with O_2 addition and CO_2 elimination) an 80% mixture of krypton with oxygen and reported changes in voice quality, a sensation of wanting to breathe more deeply, a swelling of the head, and an ill-defined but unequivocal dizziness or discomfort. It was concluded that krypton under the conditions of these experiments demonstrated no significant narcotic properties.

Later a supply of 100% xenon was made available. In view of the experiences with krypton in animals, it was decided to use rabbits as the experimental animal for xenon. A closed system was arranged to permit conservation of the gas, and to this system oxygen was added (75–100 ml/min for 2.5 kg rabbit) and CO_2 removed through soda lime. Ten rabbits were given inhalations for 15-min periods of either 80% xenon in oxygen or 80% nitrous oxide in oxygen. Equivalent but minimal narcotic effects were observed in these animals. During the inhalation there was some loss of the lid reflex, some apparent diminution in response to painful stimuli, a tendency to remain in induced unnatural postures, and a slowing of the respiration. Upon discontinuance of the inhalation, recovery was almost immediate.

Three rabbits were given 0.75 mg of morphine per kg, after which they maintained their righting reflex and demonstrated prompt response to painful stimuli. They were significantly depressed, however. During inhalation of the mixtures of either nitrous oxide in oxygen or xenon in oxygen as previously described, there was an exaggeration of the signs observed in the unpremedicated rabbits. In addition, recovery was delayed for approximately 1.5 min after discontinuance of the inhalation—i.e., the righting reflex was lost, and there was more pronounced diminution in response to painful stimuli.

Six human beings inhaled either 50% xenon in oxygen or 50% nitrous oxide in oxygen from a closed system spirometer with soda lime in the circuit. Oxygen was added according to the metabolic requirements of the individual (250–500 ml/min). Pain threshold measurements were made with the Hardy-Wolff-Goodell apparatus, and there was a uniform 15% increase in the pain threshold with either gas mixture. Each subject reported more pronounced subjective sensations of dizziness and incipient loss of consciousness with the xenon mixture than with the nitrous oxide mixture.

[1] The authors are indebted to the Linde Air Products Co. for the supply of krypton and xenon.

Two of the experimenters (SCC and EGG) inhaled a mixture of xenon in oxygen (70% Xe, 30% O_2) from the same system, and each reported pronounced narcotic effects with incipient loss of consciousness after approximately 3 min of inhalation. Recovery was prompt.

As a result of these observations, it was felt that a more critical assay of the effectiveness of xenon as an anesthetic drug could be secured by its administration to a patient for an operative procedure. Accordingly, an 81-year-old man in good physical condition was given, by means of the to-and-fro CO_2 absorption technique, a mixture of xenon in oxygen in which the oxygen concentration as measured by the Pauling meter was never lower than 18%; usually it was at least 22%.

The patient was given as premedication 0.2 mg of atropine and no analgetic or hypnotic drug. In order partially to denitrogenate the patient, he was given 100% oxygen in a semiopen system for 10 min. It was felt that this process would diminish the dilution of the xenon-oxygen mixture in the closed system. Within 3 min of the beginning of the inhalation of the xenon-oxygen mixture, the patient lost consciousness, and within 10 min the operation began. An orchidectomy was performed—an operation with a high level of painful stimulus—with no evidence of reaction to pain. During the anesthetic, the rebreathing bag was emptied three times and refilled with a fresh mixture of xenon and oxygen, to compensate for the nitrogen dilution in the closed system. Evidence such as roving eyeballs, active intercostal muscles, and the character of the respiratory pattern seemed to indicate that the patient was in first-plane third-stage anesthesia (light anesthesia). No definitive measurement of muscle relaxation could be made. There was, however, sufficient relaxation of the muscles of the jaw and pharynx to require the insertion of an oropharyngeal airway to overcome obstruction to breathing by the tongue. The pulse and blood pressure remained within normal limits for the patient, and there were no unusual respiratory patterns. Color was good, as would be expected from the satisfactory concentration of oxygen in the mixture, which was at 1 atmosphere pressure (740 mm Hg).

Upon discontinuance of the inhalation of xenon and oxygen the patient recovered within 2 min to the extent that he could identify himself and within 5 min to the extent that he could orient himself accurately and clearly. The postoperative period was uneventful.

A second patient, a 38-year-old female, was also anesthetized with xenon and oxygen. She was premedicated with 0.0004 g of scopolamine. She was induced with a mixture consisting of approximately 80% xenon and 20% oxygen. Within 5 min consciousness was lost, and within 10 min the skin incision was made. At this time she did not respond by movement to the operative manipulations but was very lightly anesthetized and had some vocalization and mild laryngeal spasm. As a consequence she was given 0.050 g of meperidine intravenously. After this she did not vocalize, had no more laryngeal spasm, and appeared by all available clinical signs to be in first-plane anesthesia. On repeated checks, the inspired oxygen concentration was above 18% and, with the exception of a few minutes, was above 22%. The breathing bag was emptied several times and refilled with the xenon-oxygen mixture to eliminate the dilution effect of nitrogen, although the patient had been denitrogenated for 10 min prior to induction of anesthesia. Blood pressure, pulse, color, and other vital signs were within normal limits. Relaxation was satisfactory, but the patient had delivered a normal full-term infant 24 hr before, and the abdomen was somewhat flabby as a consequence. The operative procedure was ligation of the Fallopian tubes, and it was reported by the surgeon that operating conditions were good. Within 2 min after discontinuance of the anesthetic, the patient responded and was able to tell that she was in the operating room. In addition, upon questioning 2 hr later, she had perfect memory for statements made within 5 min after the inhalation was stopped. Recovery has been uneventful.

This is the first time, to our knowledge, that xenon has been used as an anesthetic for an operative procedure in a human being. Its effects were at least equivalent to those that could be expected from a similar concentration of ethylene. Ethylene has a Bunsen coefficient of 1.3 in oil and 0.09 in water at 37° C with an oil-water ratio of 14.4. Nitrous oxide has a Bunsen coefficient of 1.4 in oil and 0.44 in water at 37° C with an oil-water ratio of 3.2. Ether, a much more potent anesthetic, has a Bunsen coefficient of 50 in oil and 15.4 in water at 37° C with an oil-water ratio of 3.2.

Although krypton, and particularly xenon, have appreciably higher oil-water ratios, krypton appears from the observations made to have no significant narcotic properties, and those of xenon are apparently no more prominent than ethylene. However, xenon is appreciably more soluble in oil and water than krypton. Jones reports (*4*) that the solubility of gases in blood may be a significant factor in gas exchange. This function may be more important than the oil-water ratio with respect to the ability to produce narcotic effects. In addition, Tobias *et al.* (*5*) report that there may be significant differences in the absorption of gases by the different lipoids of the body, and that the effects may be a consequence of a preferential absorption in lipoids of the central nervous system. The fact that ether has an oil-water ratio similar to that of nitrous oxide but, on the other hand, a significantly higher level of solubility in oil and water lends credence to the postulate that the total concentration in blood and intra- and extracellular fluids is an important factor in the ability of anesthetics to produce their effects.

In any event, it appears that a chemically inert gas (by current standards) is capable of producing complete anesthesia, and, although it may not by virtue of its cost of manufacture prove to be a satis-

factory agent commercially, it may materially assist in solving one of the important theoretical problems of anesthesia.

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A Simple Technique for the Identification of Raffinose and Sucrose by Enzymatic Hydrolysis on Paper Chromatograms and the Subsequent Separation of the Hydrolyzed Products by Paper Chromatography

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During studies involving the identification of sugars by paper chromatography it became necessary to verify the presence of raffinose and sucrose. The small amount of materials available necessitated a minimum amount of handling. The elution of these sugars from the chromatograms, together with their subsequent hydrolysis and concentration before rechromatographing, was undesirable. A new technique was therefore developed.

Because of the relatively rapid rate of hydrolysis of raffinose and sucrose with the enzyme invertase, it was decided to spot the sugar solution on the paper chromatogram and then superimpose the enzyme solution on the sugar spot. It was found that a microliter of solution containing 10–50 μg of raffinose or sucrose could be spotted on the paper, and partial hydrolysis of the sugar could be obtained by superimposing an equal volume of invertase solution on the sugar spot.

By experiment it was found that, if 1 μl of sugar solution was spotted on the paper, 5 μl of invertase solution immediately superimposed on the sugar spot, and the paper allowed to lie for 5 min, the hydrolysis of raffinose and sucrose was complete. The products of hydrolysis could then be partitioned as usual. The chromatographic technique was essentially that used by Partridge (*1*) and McCready *et al.* (*2*). The enzyme preparation was Difco Invertase Solution (for analytical use).[1] The chromatograms were made on Whatman No. 1 filter paper, and an *n*-butanol-ethanol-water (10–1–2) mixture served as the partitioning solvent. When the chromatogram was sprayed with the dinitrosalicylate reagent (0.5% 3,5-dinitrosalicylic acid in 5% NaOH), the melibiose and levulose from the raffinose and the dextrose and levulose from the sucrose were found to be adjacent to known pure sugars used as controls.

When the invertase solution was superimposed on only half of each of the raffinose and sucrose spots, 5 min allowed for hydrolysis, and partitioning carried out in the usual manner, additional information was obtained. When the resorcinol spray reagent (0.1% resorcinol in 0.7 *N* HCl) was used, this chromatogram revealed one half of the original raffinose spot and a part of the original sucrose spot, representing the portions of the original sugars that had not been treated with the invertase solution. In addition, levulose spots also appeared on this chromatogram as a result of the partial enzymatic hydrolysis of the original raffinose and sucrose spots. All three sugars were adjacent to known pure sugars used as controls without the addition of invertase.

This technique is being applied to sugar extracts from plant materials. It should be applicable to systems other than invertase-raffinose-sucrose.

[1] Mention of manufacturers and commercial products does not imply that they are endorsed or recommended by the Department of Agriculture over others not mentioned.

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Steroid Changes in Incubating Adrenal Homogenates[1]

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The presence of a high concentration of cholesterol in the cortex of the adrenal gland suggests an important function. It is known that under conditions of shock or administration of ACTH the adrenal cholesterol falls sharply with a concomitant increase in the release of steroids from this gland (*1*). Evidence has accumulated to indicate that cholesterol is a source compound for cholic acid (*2*), cholestenone (*3*), and progesterone. With this background it became desirable to test further the possible conversion of cholesterol to other steroids under *in vitro* conditions. The work was done throughout with whole homogenates of guinea pig adrenals. Total cholesterol was determined by a micromethod[3] devised during the course of these investigations (accuracy ±6%). Steroids were followed by use of the Zaffaroni procedure (*4*), together with the ultraviolet scanner described by Haines and Drake (*5*).

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[3] To be published.