Effects of Xenon at Elevated Pressures in the Dog

Edward F. Domino, M.D., Sheldon F. Gottlieb, Ph.D., Ralph W. Brauer, Ph.D.,
Stuart C. Cullen, M.D., Robert M. Featherstone, Ph.D.

In order to establish a general theory of anesthesia it is important to know if various anesthetic agents of diverse chemical structure have similar or dissimilar actions on the central nervous system. One means of determining more objectively the actions of various agents on different sites in the brain is through the use of the electroencephalogram (EEG). Although the origin and significance of the EEG is poorly understood it does offer empirical data which cannot be obtained in any other way. Previous EEG studies on the differential neocortical and paleocortical electrical activity of various inhalation anesthetics in the dog have demonstrated that structures such as the amygdala show marked high voltage, hypersynchronous discharge at a time when neocortical activity is depressed. The significance of this observation is that not all areas of the brain are equally affected during general anesthesia and in fact some sites show a profound synchronization of neuronal activity. Any theory of the mechanisms of anesthesia must take into account such differences in neuronal activity.

Xenon produces general anesthesia in man grossly similar to that induced by ethylene. At one atmosphere total pressure 80 per cent xenon-20 per cent oxygen mixtures are not anesthetic in the dog; this is also true for nitrous oxide. At elevated pressures xenon-oxygen mixtures may produce profound general anesthesia in the monkey. Of considerable interest is the fact that in both monkey and man rhythmic EEG activity persists to such an extent that the apparent clinical depth of general anesthesia exceeds EEG evidence of brain depression as based on EEG rating scales derived from diethyl ether and cyclopropane anesthesia. Because of these reports it seemed pertinent to determine whether xenon anesthesia is uniquely different in altering neocortical and rhinencephalic EEG activity in comparison to other anesthetic agents.

Methods

Seven adult mongrel dogs of both sexes were used in this study. Three of the animals were unanesthetized controls for purposes of establishing the parameters for general anesthesia with xenon. External EEG electrodes (lead 2) were used. The other dogs were prepared with indwelling EEG electrodes during the week prior to anesthesia with xenon. The animals were initially anesthetized with pentobarbital (30 mg./kg., intravenously) for surgery. EMG electrodes made of 32-gauge stainless steel wire were implanted in one dog. These were inserted into the pharyngeal, abdominal and gastrocnemius muscles. The EEG electrodes also were made of 32-gauge insulated stainless steel wire; this was twisted into bipolar electrodes which were bare at the tips. These electrodes were inserted into the olfactory bulb, medial amygdala and epidurally over the somatic sensory cortex using conventional techniques.

All electrical recordings were made using an Offner Type T portable polygraph. Both monopolar and bipolar EEG recordings were taken. Monopolar EEG recordings were made to a reference site below the left temporal muscle.

* Loaned by Drs. Seevers and Deneau, Department of Pharmacology, University of Michigan, Ann Arbor, Michigan.

Accepted for publication October 1, 1963. Dr. Domino is in the Department of Pharmacology, University of Michigan, Ann Arbor, Michigan; Dr. Gottlieb, Research Laboratory, Linde Company, Division of Union Carbide Corp., Tonawanda, New York; Dr. Brauer, Pharmacology Branch, U. S. Naval Radiological Defense Laboratory, San Francisco; Dr. Cullen, Department of Anesthesiology, University of California, San Francisco; and Dr. Featherstone, Department of Pharmacology, University of California, San Francisco, California. This study was supported in part by grants MY-02653, USPHS, and RG 3625, USPHS. A preliminary communication was presented at the Federation meetings.

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Table 1. Effects of Xenon in Intact Dogs

<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Simulated Depth Below Sea Level in Feet</th>
<th>Gas Concentrations in mm. Hg</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PXe = 1366, PO₂ = 566, PN₂ = 111, P₁₂₀ = 55</td>
<td>Within 30 seconds hindlimb weakness, righting reflex, biting, licking, and running movements. Convulsive-like movements for 7 minutes. No evidence of anesthesia. To descend to 66 feet.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PXe = 1181, PO₂ = 616, PN₂ = 121, P₁₂₀ = 59</td>
<td>Definite loss of RR and light surgical anesthesia; good respiratory exchange. Stage III, plane 1, anesthesia.</td>
</tr>
<tr>
<td>181</td>
<td>50</td>
<td>PXe = 999, PO₂ = 858, PN₂ = not determined, P₁₂₀ = 49.7</td>
<td>Within 3 minutes dog was excited. After 4 minutes quiet but no anesthesia. To descend to 66 feet.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PXe = 1118, PO₂ = 961, PN₂ = not determined, P₁₂₀ = 55.6</td>
<td>Three minutes later dog was very excited. Spasticity, nystagmus present. Tachypnea 38/minute. No anesthesia.</td>
</tr>
<tr>
<td>181</td>
<td>48</td>
<td>PXe = 1208, PO₂ = 841, PN₂ = 61.5, P₁₂₀ = 48.4</td>
<td>In 1 minute animal fell, limbs rigid. Constant blinking, CR+, LR+. In 2 to 4 minutes marked mastication, forelimbs were extended, hindlimbs flexed. Definite reaction to painful stimuli. Marked hyperventilation. Appears in Stage II. To descend to 58 feet.</td>
</tr>
<tr>
<td>(repeated next day)</td>
<td></td>
<td>PXe = 1429, PO₂ = 545, PN₂ = 69.2, P₁₂₀ = 54.5</td>
<td>Loss of RR, CR-sl+. Chewing movements ceased within 14 minutes. Dog definitely in surgical anesthesia after 4 minutes with CR-, PR-sl+. Stage III, plane 2.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PXe = 1638, PO₂ = 513, PN₂ = 69.5, P₁₂₀ = 59.3</td>
<td>Within 1 minute loss of RR, rolling movements, muscles rigid. Some biting movements, PR+4, CR+. Dog was anesthetized within 1½ minutes. RR-, CR- after 5 minutes.</td>
</tr>
</tbody>
</table>

The inhalation anesthetics used were diethyl ether and xenon. All animals were anesthetized at one atmosphere total pressure with open-drop ether at least one day prior to xenon anesthesia in order to perform a tracheotomy. Tracheotomy tubes (38 to 42 French) were sutured in place for administering the xenon-oxygen mixtures in a closed system. Xenon anesthesia was administered under increased pressures in a compression chamber. The compression chamber was of the type usually used by the U. S. Navy on submarine rescue barges. It was large enough to accommodate the anesthetic apparatus, two investigators and the experimental animal. Shielded wires passing through the chamber were connected to a polygraph on the outside. Viewing ports and a two way communication system allowed correlation of gross behavioral effects and the electrical recordings. Maximal pressures equivalent to 76 feet below sea level (2,508 mm. of mercury) were obtained. For convenience the pressures generally are expressed as mm. of mercury throughout the
EFFECTS OF XENON AT ELEVATED PRESSURES

The atmospheres of pressure can easily be calculated by dividing by 760. The duration and depth of the "dive" varied with the progress of the experiment. Repeated "dives" were made in accordance with standard U. S. Naval decompression tables.

The anesthetic apparatus consisted of a Benedict-Roth 9-liter spirometer and two 2-liter bags in series to act as additional gas reservoirs. The rubber bags and a unidirectional valve arrangement were essential because of the rather large dead air space in the spirometer which otherwise would readily collapse under high pressure. The reservoir bags allowed adequate ventilation. A CO₂ absorber inside the spirometer was used to prevent hypercapnia. The animal was manually restrained on the floor of the chamber and connected via tracheal intubation to the anesthetic apparatus. The following procedure was used in each case:

1. At least 5 minutes before compression control EEG and ECG recordings were taken. The animal was partially denitrogenated by allowing it to breathe 100 per cent oxygen.
2. Air compression was then begun. During this time denitrogenation continued for an additional 5 minutes.
3. When the desired air pressure was reached additional EEG and ECG recordings were obtained after which the animal was given xenon-oxygen.
4. The chamber pressure was maintained or increased, and then subsequently lowered to allow adequate observation of the signs and symptoms of anesthesia.

Gas mixtures of 60 to 90 per cent xenon in oxygen were used. The oxygen concentration was measured with a Pauling oxygen meter before and after each experiment. Furthermore, samples from the spirometer were analyzed at the conclusion of each experiment for nitrogen content. The concentration of xenon was calculated by subtracting the partial pressure of oxygen, nitrogen, and water vapor. At least 5 to 10 minutes prior to xenon anesthesia the animals were allowed to breathe pure oxygen at one or more atmospheres pressure to eliminate nitrogen from the apparatus and animals which would dilute the anesthetic mixture. No evidence of oxygen toxicity was noted during this time. Complete denitrogenation was not attempted. Subsequent to xenon studies the animals were retested using thiopental anesthesia at one atmosphere and the EEG records compared. All recording sites were confirmed histologically using the Hess iron deposition technique and subsequent staining with the Prussian blue and green reaction at the electrode tips; the nerve cells were stained with thionin.

Results

Gross Behavioral Effects of Xenon-Oxygen Mixtures. Three dogs were subjected to mixtures of 60–90 per cent xenon in oxygen given in a closed system inside the pressure chamber. At the high pressures employed even 10 per cent oxygen provided a Pox₂ sufficient to maintain adequate oxygenation. The results obtained are summarized in table 1. Such xenon-oxygen mixtures were clearly anesthetic.

A relatively high partial pressure of xenon (Pxe) was necessary to achieve general anesthesia. Partial pressures of xenon less than 1,000 mm. of mercury were not anesthetic. A marked stage of excitement was observed with a Pxe of 1,200–1,400 mm. of mercury; surgical anesthesia was observed with greater partial pressures. The animals gradually recovered from xenon anesthesia as the chamber pressure was reduced. Considerable variability was observed as to when the animal recovered from general anesthesia. One dog recovered with a Pxe around 100 mm. The other two showed some evidence of ataxia even at sea level.

Effects in Dogs with Indwelling EEG Electrodes. Four dogs were prepared with indwelling EEG electrodes. Each animal was subjected to at least one simulated dive and in several instances this was repeated on another day. One of these animals was used for a comparative study with nitrous oxide-oxygen. The pertinent data are summarized in table 2. The gross behavioral effects of xenon-oxygen mixtures in dogs with EEG electrodes were quite similar to those in animals without electrodes. It was concluded that the use of chronic indwelling EEG electrodes did not have any obvious adverse effects. For purposes of clarity the results in one of these animals will be described in detail. Dog 109 was subjected to a simulated dive of 66 feet
<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Simulated Depth Below Sea Level in Feet</th>
<th>Gas Concentrations in mm. Hg</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>260</td>
<td>76</td>
<td>( P_{\text{O}_2} = 387 )</td>
<td>Dog on back, running movements. Marked biting movements, limbs very spastic. Very transient induction hypersynchrony in olfactory bulb. No general anesthesia. Stage II.</td>
</tr>
<tr>
<td>321</td>
<td>65</td>
<td>( P_{\text{N}_2} = 458 )</td>
<td>Marked running and biting movements within 1 minute. Within 3 minutes less motor movements, RR still positive. EEG shows marked movement artifact.</td>
</tr>
<tr>
<td>74</td>
<td>65</td>
<td>( P_{\text{H}_2}\text{O} = 65.2 )</td>
<td>General anesthesia within 2 minutes. Deep surgical anesthesia with CR-, PR- and RR-. Good EEG hypersynchrony in amygdala.</td>
</tr>
<tr>
<td>64</td>
<td>60</td>
<td>( P_{\text{N}_2}\text{O} = 1317 )</td>
<td>Within 1 minute biting and convulsive-like movements. No surgical anesthesia. To descend to 75 feet.</td>
</tr>
<tr>
<td>75</td>
<td>60</td>
<td>( P_{\text{O}_2} = 447 )</td>
<td>Dog shows less muscular movements, but still biting. Within 3 minutes PR-, CR-. Good surgical anesthesia with muscle relaxation. EEG hypersynchrony in amygdala and olfactory bulb.</td>
</tr>
</tbody>
</table>

Below sea level. During this time and previously for approximately 10 minutes the dog was breathing 100 per cent oxygen. As illustrated in panel A, figure 1, the EEG showed a normal pattern of an awake animal while breathing 100 per cent oxygen at sea level. Typical low voltage, high frequency EEG activity was observed in the olfactory bulb and medial amygdala. The "respiratory bursts" usually seen in the amygdala were absent. Apparently this was related to the tracheotomy and to the lack of air flow through the nostrils. Lead 2 of the ECG showed a slight tachycardia (90 minute). As the dog was subjected to increasing atmospheric pressures in the compression chamber, the EEG remained essentially normal except for frequent electrical artifacts during movement of the animal. At a simulated pressure of 66 feet below sea level no significant EEG or ECG changes were noted. Following the administration of a xenon-oxygen mixture (\( P_{\text{Xe}} \), 1.790 and \( P_{\text{O}_2} \), 387 mm. of mercury), the animal showed loss of the righting reflex (RR) within one minute, pronounced biting movements, and some limb rigidity. Within three minutes after the initiation of xenon-oxygen inhalation the animal showed diminished biting movements. After four minutes there was pronounced muscle relaxation and obvious anesthesia. At this time the patellar reflex (PR) and corneal reflex (CR) were negative; the respiratory rate was 32/minute. The animal was estimated to be in plane 2 of surgical anesthesia. Panel B, figure 1 illustrates the animal's EEG record at that time. It may be noted that marked delta wave activity was exhibited in the olfactory bulb, somatic sensory area and the mono-
Fig. 1. Effects of xenon anesthesia on the dog EEG. Panel A: Dog breathing 100 per cent oxygen at sea level. Heart rate = 84/minute. Panel B: Dog breathing xenon-oxygen ($P_{Xe} = 1,789$, $P_{O_2} = 389$ mm. of mercury) at pressure equivalent to 66 feet below sea level. Xenon-oxygen was given for approximately 4 minutes. The animal was in deep surgical anesthesia. The corneal (CR), patellar (PR), and flexor (FR) reflexes were absent. Prior to surgical anesthesia the dog passed through a marked stage of delirium. Heart rate = 60/minute. Panel C: Continuation of xenon anesthesia. Chamber pressure equivalent to 56 feet of sea water ($P_{Xe} = 1,519$ mm. of mercury). Heart rate = 72/minute. Dog was in light surgical anesthesia. Panel D: Continuation of xenon anesthesia. Chamber pressure equivalent to 44 feet below sea level ($P_{Xe} = 1,192$ mm. of mercury). Heart rate = 84/minute. Note marked hypersynchronous activity (8 to 10 c.p.s.) especially in the amygdala leads. Much less hypersynchronous activity is present in the olfactory bulb and sensory cortex. Panel E: Continuation of xenon anesthesia. Chamber pressure equivalent to 32 feet below sea level ($P_{Xe} = 867$ mm. of mercury). Heart rate = 87/minute. Hypersynchronous activity is still present but at a much faster frequency of 12–15 c.p.s. Panel F: Recovery from xenon anesthesia. Dog breathing air at sea level for 10 minutes. Heart rate = 120/minute. Note return of fast wave EEG activity. Compare to Panel A. Symbols—OB = bipolar olfactory bulb; SS = bipolar somatic sensory cortex; AMG = bipolar cortico-medial amygdala; AMG-R = cortico-medial amygdala reference electrode below left temporal muscle. AMG-R = second cortico-medial amygdala lead to reference. All electrodes were placed in the left side of the brain. Except as designated all electrode placings were bipolar. 1:11 = lead 2 of the electrocardiogram (ECG). The designations below the ECG leads indicate the chamber pressure equivalent to feet below sea level. Each vertical bar height at the extreme right of the record in Panel B is equal to 100 microvolts and applies to all panels. Symbols are the same for all subsequent illustrations.
polar amygdala leads. The ECG showed bradycardia (heart rate 60/minute). The pressure in the chamber was then reduced to 56 feet of sea water. At this time the PX\textsubscript{e} was calculated to be 1,519 mm. of mercury. The heart rate increased to 72/minute. The EEG showed definitely less delta wave activity and some faster frequency components. This is illustrated in the record in panel C, figure 1. This record was obtained approximately 7 minutes after the induction of xenon-oxygen anesthesia. Subsequently the pressure in the chamber was reduced to a simulated depth of 44 feet. At this time the EEG, particularly in the somatic sensory area, showed lower voltage, faster frequency components and the amygdala leads (both bipolar and monopolar) showed marked 8 to 10 c.p.s. hypersynchronous activity (see panel D, figure 1). The animal was still anesthetized with a PX\textsubscript{e} of 1,192 mm. of mercury. The heart rate was now 84/minute. As the chamber pressure was decreased gradually (PX\textsubscript{e} 867 mm. of mercury) the hypersynchronous activity in the amygdala increased in frequency to approximately 12 to 15 c.p.s. The heart rate was 87/minute. At this time the dog was on his side with both the PR and CR returning to normal. As the pressure in the chamber was reduced further, the animal recovered from anesthesia while still on xenon and oxygen. In panel F, figure 1 there is shown the EEG activity of the animal breathing room air for 10 minutes after discontinuing the xenon. At this time the EEG and the ECG were essentially normal except that the heart rate was 120/minute.

One of the major problems in recording the EEG and ECG activity was artifact during the induction period of xenon-oxygen administration. Marked motor movements were obtained and the resulting artifact obscured electrical recordings. Therefore, a dog (321 studied previously; see table 2) was immobilized with succinylcholine. The animal was given 0.2 mg./kg. of succinylcholine intravenously and artificially respired with 100 per cent oxygen at sea level. The animal was then subjected to a chamber pressure equivalent to 55 feet below sea level. In figure 2 there is illustrated the EEG activity of the olfactory bulb, somatic sensory cortex, and amygdala of the animal under the various conditions listed. As might be expected EEG hypersynchrony was observed during both the induction as well as the recovery phases of xenon anesthesia. Furthermore, in this particular animal who on a previous occasion showed marked motor movements during the induction of xenon anesthesia, it is noteworthy that there was no EEG evidence during the induction period or subsequently of any cortical electrical discharge of the usual type associated with grand-mal seizures.

Comparative Effects of Other General Anesthetic Agents. All four dogs with chronic EEG electrodes were anesthetized initially with diethyl ether-oxygen to determine the EEG changes for control purposes. Tracheotomies were performed during the period of ether anesthesia. In all animals clear cut evidence of EEG hypersynchrony was observed in the olfactory bulb and the amygdala as has been described previously. For comparative purposes, the EEG changes occurring with open-drop diethyl ether-oxygen at one atmosphere in one of the animals studied are illustrated in figure 3. It is to be emphasized that these are the same EEG electrode sites from which recordings were made during xenon anesthesia. Differences between the EEG effects of diethyl ether and xenon exist in that xenon anesthesia caused considerably more delta wave activity than was evident with diethyl ether (compare figures 2 and 3). This observation was noted in all four dogs studied.

One animal (dog 64) was given nitrous oxide-oxygen at increased pressures for purposes of comparison with xenon. At one atmosphere total pressure 80 per cent nitrous oxide-20 per cent oxygen mixtures (PX\textsubscript{NO\textsubscript{2}} = 608 and PO\textsubscript{2} = 152 mm. of mercury) do not produce anesthesia in most dogs. This particular animal was subjected to a pressure equivalent to 75 feet below sea level. The PX\textsubscript{NO\textsubscript{2}} was 1,538 and the PO\textsubscript{2} 447 mm. of mercury (see table 2). It can be concluded that nitrous oxide-oxygen under high pressure is clearly anesthetic and resembles the effects obtained with xenon under similar circumstances.

All four animals were subsequently given 30 mg./kg. of thiopental as an intravenous infusion over approximately three minutes. During this time the EEG was recorded con-
Fig. 2. Effects of xenon anesthesia on the EEG of a dog immobilized with succinylcholine. 
Panel A: Dog was paralyzed with 0.2 mg./kg., of intravenous succinylcholine and artificially 
respired with 100 per cent oxygen at a chamber pressure equivalent to 55 feet below sea 
level. Panel B: One minute after the administration of 90 per cent xenon and 10 per cent 
oxygen at a chamber pressure equivalent to 55 feet below sea level (P<sub>x</sub> = approximately 
1,831, P<sub>O2</sub> = 202 mm. of mercury). Panel C: One minute and twenty seconds after the in-
duction of xenon anesthesia. Note the appearance of hypersynchronous activity in the amyg-
dala and olfactory bulb and delta wave in somatic sensory cortex. Panel D: One minute and 
fourty seconds after the induction of xenon anesthesia. Note disappearance of fast frequency 
EEG hypersynchrony and appearance of delta wave activity as the depth of anesthesia in-
creases. Panel E: Two minutes after induction of xenon anesthesia. Note the marked delta 
wave activity throughout the EEG record. Panel F: Lightening of general anesthesia produced 
by reducing chamber pressure from a simulated depth of 55 feet to 52 feet. Note the 
reappearance of hypersynchronous activity of approximately 9 c.p.s. in the amygdala. Panel 
G: At a chamber pressure equivalent to 52 feet below sea level the hypersynchrony is again 
reappearing at a frequency of approximately 20 c.p.s. Panel H: The chamber pressure was 
reduced to 45 feet below sea level. Note the development of hypersynchrony in olfactory 
bulf at this time. Panel I: The chamber pressure was now reduced to 20 feet below sea 
level. Note the marked reduction of hypersynchronous activity in the amygdala and return 
of more normal EEG activity. Panel J: Dog breathing air at sea level. Note return of normal 
EEG activity. Symbols and abbreviations used for this figure are similar to those in figure 1.
continuously. During the initial administration of thiopental typical barbiturate fast-wave activity was observed in all EEG leads. As the dose of thiopental increased, generalized high voltage, delta wave activity was observed. Under these circumstances it was not possible to reproduce as clearly hypersynchronous EEG activity in either the olfactory bulb or the amygdala.

**Effects of Xenon Anesthesia on the ECG.** Pittenger *et al.*² have reported that xenon anesthesia produces a bradycardia in the monkey. Occasionally we have observed a similar phenomenon in the dog. Table 3 presents the variable effects of xenon anesthesia on the heart rate of the dogs studied. To a large extent the variability was related to the depth of xenon anesthesia and to the degree of initial excitement. Some animals such as dogs 109 and 321 showed a marked bradycardia during the peak P xe. In all animals a definite tachycardia was observed following withdrawal of xenon. Other ECG changes were observed frequently during xenon anes-

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**Fig. 3.** Effects of diethyl ether anesthesia on the dog EEG. **Panel A:** Same animal and electrode recordings as in figure 2. The dog was breathing room air. Note occasional high frequency bursts in the amygdala of this animal before the tracheostomy was performed. These respiratory bursts were absent after the tracheostomy (see control figure 2). **Panel B:** Three minutes after beginning ether-oxygen the animal was in surgical anesthesia. **Panel C:** Four minutes after beginning ether-oxygen. **Panel D:** Five minutes after beginning ether-oxygen. The animal was in deep surgical anesthesia at this time. The CB, RR and PR were absent. Symbols and abbreviations are similar to those of figure 1.
Table 3. Effects of Xenon Anesthesia on the Heart Rate per Minute

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>Heart Rate on Room Air</th>
<th>Heart Rate on Oxygen</th>
<th>Peak Pxe (mm. Hg)</th>
<th>Heart Rate at Peak Pxe</th>
<th>Heart Rate After Withdrawal of Xenon</th>
</tr>
</thead>
<tbody>
<tr>
<td>105</td>
<td>—</td>
<td>81</td>
<td>1484</td>
<td>96</td>
<td>174</td>
</tr>
<tr>
<td>181</td>
<td>—</td>
<td>—</td>
<td>1428</td>
<td>111</td>
<td>144</td>
</tr>
<tr>
<td>305</td>
<td>—</td>
<td>111</td>
<td>1638</td>
<td>108</td>
<td>120</td>
</tr>
<tr>
<td>109</td>
<td>90</td>
<td>84</td>
<td>1780</td>
<td>60</td>
<td>126</td>
</tr>
<tr>
<td>260</td>
<td>72</td>
<td>84</td>
<td>1307 (stage II only)</td>
<td>120</td>
<td>90</td>
</tr>
<tr>
<td>321</td>
<td>—</td>
<td>87</td>
<td>2017</td>
<td>78</td>
<td>153</td>
</tr>
<tr>
<td>321 (repeat under Succinylcholine)</td>
<td>84</td>
<td>72</td>
<td>1831</td>
<td>36</td>
<td>114</td>
</tr>
<tr>
<td>64</td>
<td>78</td>
<td>72</td>
<td>Pnx40 = 1538</td>
<td>114</td>
<td>150</td>
</tr>
</tbody>
</table>

Thesia. These consisted of a widening of the QRS complex. There were no consistent trends that could be related conclusively to the administration of xenon rather than to possible positional effects. One animal in deep xenon anesthesia received 10 μg./kg. of epinephrine, intravenously, in an attempt to obtain evidence of sensitization of the heart by xenon. With the administration of this large dose of epinephrine a very marked tachycardia was elicited; ventricular fibrillation was not obtained. Repeated doses of epinephrine failed to produce ventricular fibrillation in this dog anesthetized with xenon.

Effects of Xenon on the EMG. A few of the animals had EMG electrodes placed in the muscles of the neck, the rectus abdominus and the gastrocnemius muscles. During induction of xenon anesthesia a very marked increase of EMG activity was observed in all muscles. When second stage motor activity was marked an increase in EMG activity was observed. During deep xenon anesthesia there was a diminution of EMG activity in the leg muscles. However, the strap muscles of the neck and the rectus abdominus continued to show EMG activity that was related to the marked tachypnea frequently observed with light xenon anesthesia.

Histological Studies. The brains of the dogs with chronically indwelling electrodes were examined both grossly and histologically to verify the electrode sites. In general the somatic sensory cortex leads were in the postcruciate gyrus, usually in the trunk or leg area. The olfactory bulb lead showed the greatest variability of placement. Most of the animals had leads in the olfactory bulb or olfactory tract. All of the amygdala electrodes were in the cortico-medial nuclear group of the amygdala.

Discussion

Sixty to 90 per cent mixtures of xenon in oxygen at elevated pressures were anesthetic in the dog. Some variability was observed in the Pxe necessary to produce general anesthesia. Denitrogenation of the animals by the prior administration of 100 per cent oxygen apparently was incomplete because definite concentrations of N₂ were present perhaps because the apparatus was not completely leakproof. Xenon at a calculated pressure of 1,600 mm. of mercury or more invariably produced anesthesia. A marked stage of excitement was observed in all animals. This could be diminished considerably by increasing the partial pressure of xenon and hence would not appear to be specific for this agent.

Hypersynchronous electrical activity was noted in the olfactory bulb and amygdala which resembled that observed with other inhalation anesthetics such as diethyl ether and nitrous oxide. During the administration of deep xenon anesthesia the neocortical leads showed increased voltage and marked delta wave activity. Pittinger et al. have observed that there appears to be much more depres-
tion of the neocortical EEG in monkeys than might be expected from other estimates of the depth of anesthesia. A similar phenomenon appears to be true in the case of xenon when it is compared to diethyl ether anesthesia in the dog. Considerable delta wave activity was observed with xenon, particularly in the somatic sensory cortex; this was not observed with diethyl ether even though the estimated depths of general anesthesia were roughly comparable.

In view of the fact that xenon-oxygen mixtures are not odoriferous and are non-irritating in man, it appears that the hypersynchronous activity observed in the olfactory bulb and amygdala of the dog is related to general anesthesia and not to the irritant or possible odoriferous properties of the general anesthetic. Of course xenon may have such properties in the dog whose olfactory sense is more acute. Nevertheless, numerous inhalation anesthetics with widely divergent odors produce similar wave forms at the proper depth of anesthesia. Interestingly, it was not possible to show any hypersynchronous activity when thiopental was administered. The initiation of hypersynchrony in these structures is more likely with inhalation anesthetics than the barbiturates. EEG hypersynchrony appears at a specific level of general anesthesia and subsequently diminishes in frequency as the depth of anesthesia increases. During anesthesia with xenon it was usually associated with the lightening of anesthesia resulting from reduction of the chamber pressure. The hypersynchronous activity varied in frequency from a low of approximately 8 to 10 c.p.s. with deep xenon anesthesia to a high of 30 or more c.p.s. during light xenon anesthesia.

Various types of high frequency bursts were recorded from the amygdala. One type is that seen during stressful states in unanesthetized animals and man (see discussion by Brazier, pages 163–164 in Abramson 7). These bursts are related to an increase in the depth of respiration and, thus, to airflow through the nostrils.8 A second type of hypersynchronous waves of greater duration are those recorded during general anesthesia as described in this and a previous study.9

Inasmuch as animals without chronically indwelling electrodes showed similar marked induction delirium the marked second stage of xenon anesthesia seems not to be related to brain damage. One animal given nitrous oxide under similar conditions of increased pressures showed a similar stage of delirium. Hypersynchronous activity also was seen in the olfactory bulb and amygdala during surgical anesthesia with nitrous oxide. The impression was that xenon compared favorably to nitrous oxide. This would confirm previous observations that xenon is equipotent or more potent than nitrous oxide.

The bradycardia reported by Pittinger et al.5 was not consistently observed in the dog. Those animals subjected to deep xenon anesthesia had the most consistent decreases in heart rate. All animals showed a significant tachycardia upon recovery from xenon anesthesia, which may be related to excitement, to the release of catecholamines, or simply to removal of the pharmacological effects of xenon.

Although xenon has been shown to react chemically with fluorine to form xenon tetrafluoride,9–11 interest in the anesthetic properties of xenon continues unabated for it is unlikely that xenon can be involved in any significant chemical reactions in the living organism. It would appear in our present state of knowledge that xenon affects biological systems primarily via van der Waals’ forces, probably of the dipole-induce dipole type.12 The importance of this is that, in spite of being a symmetrical atom with no potential for forming chemical bonds in biological systems, xenon produces general anesthesia. The wide variety of seemingly unrelated chemical agents which produce overtly somewhat similar general anesthesia strengthens those hypotheses which emphasize the physical mechanisms of anesthesia. Our studies indicate that the inhalation anesthetics produce similar electrical phenomena especially in the rhinencephalic structures if the depth of anesthesia is proper. At equal depths of anesthesia induced by various inhalation anesthetics, the electrical activity of the cerebral cortex is much more variable. Nevertheless, the overall findings tend to support any molecular theory which encompasses a common mechanism for all of these substances.
SUMMARY

(1) Xenon is anesthetic to the dog at a partial pressure of 1,600 ± 200 mm. of mercury.

(2) As with other inhalation anesthetics, the rapidity of induction with xenon appears to be directly dependent upon the partial pressure.

(3) Xenon in anesthetic tensions produces EEG changes similar to those of other inhalation anesthetics. These include marked high voltage \textit{delta} wave activity in the somatic sensory cortex which was greater with xenon than with diethyl ether at comparable depths of anesthesia in the same dog. Hypersynchronous high voltage activity was noted especially in the amygdala during induction and recovery from deep xenon anesthesia. This is true also with diethyl ether.

(4) Following rapid induction of thiopental anesthesia high voltage hypersynchronous EEG activity, as seen with inhalation anesthetics, was not observed.

(5) It is concluded that the hypersynchronous EEG activity is due to the depth of general anesthesia and not to the inhalation anesthetic \textit{per se}. The findings are compatible with any theory of general anesthesia that proposes a common mechanism for the inhalation anesthetics studied.

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