Ventilatory Responses to Hypercapnia and Hypoxia at Normothermia and Moderate Hypothermia During Constant-Depth Halothane Anesthesia

Michael J. Regan, M.D.,* and Edmond I. Eger, II, M.D.†

Ventilatory responses of dogs to hypercapnia and hypoxia were studied at 37° C, 32° C, and 28° C during constant-depth halothane anesthesia. Minute ventilation fell from 4.9 liters/minute at 37° C, to 2.5 liters/minute at 28° C, and returned to 3.7 liters/minute at 37° C. Resting Paco₂ decreased from 47 mm. of mercury to 39 mm. of mercury and return to 49 mm. of mercury. At 37° C, minute ventilation increased by 380 ml. per mm. of mercury increase in Paco₂. At 32° C, this decreased to 160 ml. per mm. of mercury, and at 28° C to 100 ml. per mm. of mercury. Ventilatory responses returned to 260 ml. per mm. of mercury at 32° C, and 380 ml. per mm. of mercury at 37° C. At 37° C, ventilation increased from approximately 4 liters/minute at a Paco₂ of 400 mm. of mercury to 15 liters/minute at 30–40 mm. of mercury. At 28° C, ventilation increased by only 1–2 liters/minute for a similar change in Paco₂. These data suggest that the anesthesiologist maintain even greater vigilance over his patient during hypothermia since the usual clinical clues are obscured should hypercapnia or hypoxia develop.

The ventilatory response of hypothermic anesthetized animals to hypercapnia has been measured by several investigators with differing results. Cranston et al.¹ compared the ventilation of anesthetized normothermic and hypothermic dogs during inhalation of 6 per cent CO₂ in air and concluded that during hypothermia the ventilatory response was not different from that observed during normothermia. Salzano and Hall,² on the other hand, showed a markedly depressed response of anesthetized dogs at 29° C to inhalation of 4 per cent and 5.5 per cent CO₂ in air.

Ventilatory responses to hypoxia during hypothermia have also been determined with conflicting results. Nashat et al.³ for example, described a feeble respiratory response of anesthetized cats at 28° C to inhalation of 10 per cent O₂–90 per cent N₂ mixtures. Terzioglu,⁴ on the other hand, found in anesthetized dogs at 28° C that the ventilatory response to hypoxia approached that seen during normothermia.

In none of the studies were the respiratory effects of hypoxia and hypercapnia investigated in the same animal. In addition, previous studies of hypoxia gave little or no attention to the control of Pco₂. Similarly, those who measured responses to carbon dioxide inhalation did not control Po₂.

The greatest obstacle to interpretation of data from the above studies is the diversity of anesthetic agents and techniques employed. Usually thiopental, pentobarbital, or a longer acting barbiturate was used for induction with repeated injections if the animal shivered or showed signs of awakening. Assessment of anesthetic depth was difficult. Finally, failure to recognize the decreased concentration of anesthetic required with decreasing body temperature made comparison of results in the same animals less valid, since variation in anesthetic depth affects respiration and respiratory responses to hypercapnia and hypoxia.

A technique of constant-depth halothane anesthesia has been described recently, which

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Accepted for publication February 21, 1966.

This work was supported in part by United States Public Health Service Grants 5-K3-GM-17, 685-03; HE 07946-02; and 5T1-GM-63-07.
simplifies the problem of maintaining a steady state of anesthesia. Eger et al.5 determined the minimum alveolar concentration (MAC) of halothane necessary to prevent gross purposeful movement in response to a standard painful stimulus and to produce a light, reproducible, surgically useful plane of anesthesia. A rectilinear fall in MAC was demonstrated when body temperature decreased to 28° C., MAC at this level approaching one-half the value observed at 37° C. This finding makes it possible to maintain comparable anesthetic “depths” at different temperatures. The present investigation was undertaken to learn more of the animals’ responses to hypercapnia and hypoxia during moderate hypothermia (28° C.). Since there are scant data describing responses between 28–37° C. observations were also made at an intermediate hypothermic level (32° C.).

Materials and Methods

Seven adult male mongrel dogs weighing from 14 to 17.1 kg. were studied, with no premedication. Anesthesia was induced with a halothane-oxygen mixture at flows of 1–2 liters per minute into a circle system. A carbon dioxide absorber with variable bypass was included in the system. When anesthesia was attained a cuffed endotracheal tube was inserted, and the anesthetic inflow rate was decreased to 1 liter/minute. Animals breathed spontaneously throughout the experiment.

End-tidal halothane concentration was continuously monitored with a Rahn sample and Analytic Systems ultraviolet halothane analyzer. Total dead space of the endotracheal tube and valves of the Rahn sampler was 55 ml. and remained constant throughout the experiment. Expired gas volume was measured with a recording ventilator.7 Volumes were corrected to BTPS. End-tidal carbon dioxide tension was measured with a Beckman-Spincio Model LB-1 infrared analyzer, and inspired oxygen tension with a Beckman-Pauling oxygen analyzer, Model D. Esophageal temperature was continuously measured with a thermistor-probe electrode and Yellow Springs telethermometer.

End-tidal halothane concentration at normothermia was maintained between 0.95 and 1.15 per cent, or slightly above MAC (0.87 ± 0.12 per cent).2 This concentration was reduced to 0.75–0.85 per cent at 32.3° C. and 0.52–0.65 per cent at 28.0° C. End-tidal concentration for any one animal was held within a 0.1 per cent range. Observations were made after 15 minutes at constant end-tidal halothane concentration to allow at least 95 per cent brain-blood (alveolar) equilibration.

Hyperinflation of the lungs was carried out periodically to minimize alveolar collapse and resultant venoarterial shunting.9 The individual experiments usually lasted from 12 to 16 hours. All animals received from 1,000 to 1,500 ml. of 5 per cent dextrose in Ringer’s lactate solution infused slowly into a femoral vein. Arterial samples were obtained anaerobically in 5 ml syringes whose cylinders and plungers were coated and dead spaces filled with heparin (1,000 units/ml.). Arterial carbon dioxide tension was measured with a Severinghaus Pco2 electrode, oxygen tension with a modified Clark P02 electrode, and pH with a Radiometer pH electrode. Arterial blood pH, Pco2, and P02 values were corrected to the temperature of the animals at time of sampling.10

Response to hypercapnia was recorded at 2 levels of increased arterial carbon dioxide tension. A period of steady-state control resting ventilation was recorded, and a sample of arterial blood withdrawn. Inspired carbon dioxide tension was then increased 10–20 mm. of mercury by bypassing the carbon dioxide absorber and by adding carbon dioxide to maintain end-tidal carbon dioxide tension constant for at least 6–8 minutes to allow brain-blood equilibration.11 Arterial blood was withdrawn during the last minute of ventilation at this Pco2 and minute ventilation recorded. End-tidal carbon dioxide tension was again increased and then maintained at a higher level, and this sequence was repeated. The carbon dioxide absorber was then reintroduced into the system, ventilation and end-tidal tension were allowed to return to control values, and another control arterial blood sample obtained after 6 minutes of constant end-tidal Pco2. Arterial oxygen tension throughout this time was maintained above 300 mm of mercury.

Following this, in 5 dogs observations of the ventilatory response to hypoxia were made.
Table 1. Summary of Results

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>37.3 ± 0.5</th>
<th>32.3 ± 0.5</th>
<th>28.0 ± 0.2</th>
<th>32.3 ± 0.4</th>
<th>37.0 ± 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-tidal halothane (%)</td>
<td>1.04 ± 0.10</td>
<td>0.77 ± 0.04</td>
<td>0.50 ± 0.87</td>
<td>0.81 ± 0.14</td>
<td>1.06 ± 0.11</td>
</tr>
<tr>
<td>Resting V&lt;sub&gt;E&lt;/sub&gt; (L/min.)</td>
<td>4.9 ± 1.7</td>
<td>4.8 ± 2.1</td>
<td>2.5 ± 1.1</td>
<td>3.4 ± 0.8</td>
<td>3.7 ± 1.1</td>
</tr>
<tr>
<td>Resting Paco&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>46.0 ± 3.5</td>
<td>38.9 ± 8.8</td>
<td>38.8 ± 8.8</td>
<td>39.0 ± 1.0</td>
<td>40.2 ± 3.8</td>
</tr>
<tr>
<td>Resting pH</td>
<td>7.400 ± 0.046</td>
<td>7.427 ± 0.053</td>
<td>7.403 ± 0.034</td>
<td>7.414 ± 0.060</td>
<td>7.438 ± 0.047</td>
</tr>
<tr>
<td>Base Excess (mEq/L)</td>
<td>0 ± 3.4</td>
<td>0.5 ± 2.2</td>
<td>-0.9 ± 4.7</td>
<td>0 ± 2.5</td>
<td>0.5 ± 2.5</td>
</tr>
<tr>
<td>Mean CO&lt;sub&gt;2&lt;/sub&gt; response slope (L/min./mm. Hg)</td>
<td>0.38 ± 0.18</td>
<td>0.16 ± 0.08</td>
<td>0.10 ± 0.06</td>
<td>0.26 ± 0.22</td>
<td>0.38 ± 0.33</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation.

Oxygen flow into the system was decreased, and nitrogen added in flows of 1–1.5 liters/minute to maintain inspired oxygen tension between 10–12 per cent for 4–6 minutes. The ventilatory response during the last minute was recorded and an arterial blood sample withdrawn. Inspired oxygen tension was then decreased further, held between 5.5–7.5 per cent for 4–6 minutes, and another arterial specimen obtained. If the animals hyper-ventilated during these periods of hypoxia, the carbon dioxide absorber bypass was used to maintain end-tidal carbon dioxide tensions as near to the control resting value as possible. Following this, the carbon dioxide absorber was reintroduced into the anesthetic circle, flow of nitrogen stopped, and oxygen increased to 5–6 liters/minute for 2–3 minutes and 1 liter minute thereafter. Repeat observations of ventilation and of arterial blood gases were made after return to control ventilation.

These observations were repeated at two levels of hypothermia, 32.3° C. and 28.0° C. Hypothermia was induced by surface cooling with ice requiring 60–80 minutes. Observations were made after stabilization for 20–30 minutes at the desired temperature. The animals were rewarmed with heating pads. Observations were then repeated at 32.3° C. and 37.0° C. For the re-warming phase, 6 of the 7 animals originally studied were considered adequate subjects. One animal was dropped from the study because of neurologic damage from an inadvertently prolonged and severe hypoxic observation period at 28.0° C.

In 3 dogs, lung and chest wall compliances were measured. A thin-walled latex balloon filled with 0.5 ml. of gas was placed in the esophagus. A different pressure transducer allowed a comparison of this pressure with that taken from the airway. Airway pressure was directly measured with a water manometer. Lung inflations of 500 ml. from a calibrated syringe along with concomitant pressure measurements permitted measurement of lung and total (lung and chest wall) static compliances.

Individual ventilatory response slopes to CO<sub>2</sub> were assumed to be linear in the P<sub>CO<sub>2</sub></sub> range studied and were calculated by the method of least squares. Mean slopes were derived as the arithmetic average of individual slopes and were drawn through a mean P<sub>CO<sub>2</sub></sub> and ventilation point.

Results

Table 1 summarizes the measurements at each temperature. Except in one instance to be discussed later, the end-tidal halothane concentrations for any one dog were the same at any temperature during cooling and re-warming. Resting minute ventilation (V<sub>E</sub>) fell progressively from 4.9 liters/minute at 37.3° C. to 2.5 liters/minute at 28° C. and rose to 3.7 liters/minute on return to 37° C. Despite the decrease of ventilation at 28° C., resting P<sub>4</sub><sub>CO<sub>2</sub></sub> fell from 46.6 mm. of mercury at 37.3° C. to 38.8 mm. of mercury at 28° C. P<sub>4</sub><sub>CO<sub>2</sub></sub> rose again to 49.2 mm. of mercury upon re-warming to 37° C. Arterial pH rose during cooling from 7.36 at 37.3° C. to values between 7.40 and 7.43 at the lower temperatures and fell to 7.35 on re-warming to 37° C. The mean base excess was maintained be-
between +1 and −1 mEq./liter. Neither $V_E$, $P_{CO_2}$, pH, nor base excess at 37° C., after rewarming, was significantly different from the initial values at 37° C. before cooling ($P > 0.05$, paired t test).

The mean slope of the ventilatory response curve to CO$_2$ also decreased progressively during cooling (from 0.38 liters/minute/mm. of mercury to 0.10 liters/minute/mm. of mercury) and increased again during rewarming (to 0.38). This is shown in the table and in figures 1 and 2. Figure 3 illustrates the changes in individual slopes as a function of body temperature. In three instances (dogs 4

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**Fig. 1.** Changes in ventilatory responses to hypercapnia during cooling.

**Fig. 2.** Changes in ventilatory responses to hypercapnia during rewarming.
and 27–37°C. during rewarming are both significant (P < 0.05, paired t test).

Responses to hypoxia are presented in figures 4 and 5. The marked depression of ventilatory reactivity at 28°C is evident and is even more noteworthy since arterial oxygen tensions reached were lower than those at normothermia (32.5 ± 4.2 mm. of mercury versus 38.8 ± 5.4 mm. of mercury). As mentioned above, we attempted to maintain arterial P_{CO_2} at resting levels throughout the hypoxic periods. Table 2 presents the average deviation from resting values of P_{CO_2} during these periods showing that those observed were small, ± 2 mm. of mercury at most temperatures. More significantly, most of the average deviations at lower temperatures were positive, while those at normothermia were negative. These circumstances should have led to a decreased ventilatory response at normothermia and an increased response at hypothermia. The opposite occurred, emphasizing the depressive effect of hypothermia on the hypoxic response.

Compliance measurements are given in table 3. Slight but consistent decreases were noted with decreasing temperatures.

Discussion

Response to Hypercapnia. The results of the present investigation demonstrate a reversible reduction in ventilatory responsiveness to CO_{2} with hypothermia despite constant anesthetic depth. This reduction is progressive with falling body temperatures.

We wished, in this phase of the experiment, to simulate the usual anesthetic situation in regards to an enriched inspired oxygen concentration. Thus, arterial P_{O_2} was kept above 300 mm. of mercury at all temperature levels.

<table>
<thead>
<tr>
<th>Deviations (mm. Hg) during</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.0</td>
</tr>
<tr>
<td>Hypoxic mid-point</td>
<td>0.6 ± 3.9</td>
</tr>
<tr>
<td>Hypoxic low-point</td>
<td>-0.1 ± 3.1</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation.
Fig. 4. Changes in individual ventilatory responses to hypoxia during cooling. The lines drawn from point to point are not intended to define continuous ventilatory response curves but to facilitate following the individual responses relative to their control points.

Fig. 5. Changes in individual ventilatory responses to hypoxia during rewarming.
TABLE 3. Compliance

<table>
<thead>
<tr>
<th>Compliance (L/cm H2O)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37.3</td>
</tr>
<tr>
<td>Lung</td>
<td>0.071</td>
</tr>
<tr>
<td>Lung and chest wall</td>
<td>0.039</td>
</tr>
</tbody>
</table>

This virtually eliminated the hypoxic respiratory drive from peripheral chemoreceptors although there is slight activity even at this level of PaO₂. Moreover, this elevated PaO₂ probably depressed, to some extent, the slope of ventilatory response to CO₂. Evidence from Cunningham et al. indicates that in an awake man the slope may be depressed 10–20 per cent by raising PaO₂ from 100 to 350 mm of mercury, with little further change between 350 and 600 mm of mercury. Data from anesthetized animals are lacking, but the depression may exist there, too. However, this should not have contributed to the slope decreases we observed at lower temperatures since PaO₂ was kept above 300 mm of mercury at all temperature levels.

Our findings agree generally with those of Salzano and Takeshi, who observed diminished ventilatory responses to CO₂ at 28°C. In both these studies, initial normothermic and subsequent hypothermic slope values were lower than those we observed and probably reflect different anesthetic techniques and agents (intravenous Dial, urethane or pentobarbital). Our results differ from those of Cranston et al. who could demonstrate in anesthetized dogs no difference in response at 37.5°C and 26°C. However, these animals were premedicated with morphine and initial slopes were low. Subsequent depression from hypothermia was probably difficult to demonstrate.

We observed variable response slopes among the animals at isothermic levels. This may relate to differing anesthetic depths attained in each animal relative to the MAC value for that animal. We made no attempt to determine this figure in each dog and it is likely that MAC varied over the range 0.77–1.01 per cent halothane as described. Once chosen for an animal, the halothane dose relative to MAC was kept constant at each temperature level with one exception (dog 2). Here halothane concentrations upon rewarming were inadvertently held 20 per cent below those maintained initially. This lower concentration probably gave rise to the steeper slopes observed during rewarming.

Mean resting ventilation at 28°C fell to 50 per cent of the normothermic ventilation, while resting PaO₂ simultaneously declined approximately 17 per cent. Assuming a stable respiratory quotient, these figures suggest that the mean metabolic rate decreased more than 50 per cent, since with metabolic rate unchanged, the PaO₂ should have been double. This agrees with previous reports of approximately 55 per cent reduction for a similar fall of body temperature. Our estimate is only approximate since the respiratory quotient may fall during hypothermia. Moreover, alveolar ventilation was not measured. This makes precise estimates of metabolic rate reduction impossible because of the increase in anatomic dead space which develops during moderate hypothermia.

As table 1 indicates, resting ventilation maintained the PaCO₂ lower during hypothermia even though ventilatory responsiveness to CO₂ challenge was markedly depressed. The reason for this disparity between adequate resting ventilation and depressed CO₂ responsiveness is obscure. One possibility is a decrease in lung or chest wall compliance. A decrease during cooling might decrease the ventilatory responsiveness to CO₂ yet hardly affect resting ventilation. Lung and chest wall compliance, however, did not change appreciably during the course of the study.

Another possibility exists and is perhaps more likely. Mitchell et al. have located paired areas sensitive to H⁺ on the ventrolateral surface of the medulla of the cat. These areas are superficial and are distinct from the classic respiratory center which lies 5–6 mm deeper in the medulla. There is reason to believe that these areas are major sites of medullary chemosensitivity, and they have been termed intracranial chemoreceptors. Perforating them with acidic mock cerebrospinal fluid (CSF) caused hypopnea and with alkaline mock CSF hypopnea. Flooding these areas...
with cold mock CSF reduced ventilation promptly, and apnea usually occurred when the medullary surface temperature fell below 20°C. This suggests that the waning ventilatory responsiveness to CO₂ during moderate hypothermia may result from cold depression of these intracranial chemoreceptors. As cooling progresses other sensory stimuli may then replace the depressed chemical drive so that resting ventilation is maintained. This might account for the disparity between adequate resting ventilation and feeble responsiveness to CO₂. The nature of these other sensory stimuli is unknown. Perhaps the peripheral (dermal) stimulation of a cold environment overbalances the central chemoreceptor depression by cold.

Metabolic acidosis develops during hypothermia unless shivering is avoided. In an effort to maintain a stable base excess, 5 per cent dextrose in Ringer's lactate solution was infused to maintain the level between +1 and −1 mEq/liter. Hence, in line with changes in Pa₄₀₂ and the known effects of cold on the pK of and solubility of CO₂ in blood, the pH rose during cooling and fell again after rewarming.

Response to Hypoxia. These studies demonstrate a marked depression of the ventilatory response to hypoxia during hypothermia, a finding in agreement with Nashat’s observations of a feeble reaction in cats. Terzioglu et al. reported only moderately diminished responses at hypothermic levels when they were related to the resting ventilation at these temperatures. Since, in the latter study, minute ventilation during hypothermia approached only 60 per cent of the normothermic value, the absolute ventilatory response was much lower.

In comparing our studies with these, dissimilar anesthetic technique has already been mentioned. Also, our animals breathed high oxygen mixtures during control periods to prevent hypoxia and approximate the usual clinical anesthetic situation, whereas other investigators used room-air. Arterial P_C₇₀₂ was held stable throughout the hypoxic period in our study, while mild hypocapnia occurred in previous studies. Both these variations in experimental technique should, if anything, have increased the ventilatory responses we observed at lowered P_O₂. However, those observed during hypothermia were feeble indeed.

Our experimental conditions may have diminished the effectiveness of the hypoxic stimulus during hypothermia. The resting arterial P_C₆₀₂ values were significantly less during hypothermia than during normothermia. Since the P_C₆₀₂ during the hypoxic stress was held at the resting level, the respiratory responses to hypoxia during hypothermia were determined against a background of lower carbon dioxide tension. Since hypoxia and hypercapnia act synergistically on ventilation, this may have lowered the ventilatory response to the decreased P_A₄₀₂. Nevertheless, since P_C₆₀₂ values were those obtained during spontaneous ventilation, they would likely also be those occurring during any clinical hypoxic stress.

The ventilatory response to hypoxia is due to peripheral chemoreceptor stimulation, largely carotid body stimulation. The depressed ventilatory responsiveness to hypoxia during hypothermia may have been the effect of cold on the carotid body. In support of this, Bernthal and Weeks perfused the isolated carotid bodies of anesthetized normothermic dogs with cold blood, and showed a progressive reduction of resting ventilation. With the perfusant blood at 15–16°C., a 34 per cent fall in resting ventilation was found. They did not maintain alveolar or arterial P_C₆₀₂ at normothermic levels, so the reduced ventilation during cold-perfusion probably represents the net effect of cold-depression and hypercapnic stimulation. They suggested that during cold-perfusion carotid body metabolism was depressed and local production of acid metabolite reduced. Thus, they postulated, led to diminished peripheral input to the respiratory center which accounted for the decrease in ventilation. Schmidt et al. confirmed these findings and extended the cold-perfusion studies using CO₂-free phosphate-buffered Locke’s solution at pH 7.5 saturated with oxygen (P_O₂ > 150 mm. of mercury). The results were similar. Thus, aside from an effect on local metabolite production, cold could have a more direct effect on the carotid body, possibly through temperature receptors.
Specific temperature receptors have, however, not yet been demonstrated.

Depression of nerve conduction in the carotid and glossopharyngeal nerves and in motor pathways to the respiratory muscles may also have contributed to the decreased responsiveness. However, this is unlikely since action potentials are minimally diminished in homeotherms at 28°C and conduction velocity is still 75–80 per cent of the normothermic velocity. Action potentials in C fibers are also well maintained at 28°C, and conduction velocity at this temperature is probably also maintained.

Direct depression of the respiratory center is also improbable since resting ventilation was well maintained during hypothermia. It is unlikely that at colder body temperatures hypoxia is more directly depressive to the respiratory center. Since brain tissue oxygen needs are less during hypothermia, the depressive effect of hypoxia should likewise be less.

The markedly diminished respiratory response to increased carbon dioxide or decreased oxygen during hypothermia calls for greater vigilance at these lower temperatures. Although the organism can better tolerate reduced oxygen concentrations at lower temperatures because of decreased metabolism, caution should be exercised. There is little ventilatory warning of the development of hypoxia or hypercapnia.

Summary

Ventilatory responses of dogs to hypercapnia and hypoxia were measured during normothermia and at two levels of moderate hypothermia. A technique of constant-depth halothane anesthesia was employed. Minute ventilation and resting control PaCO2 fell with decreasing body temperatures. In addition, a progressive decrease in ventilatory responsiveness to both increased CO2 inhalation and decreased O2 inhalation was observed so that at 28°C responsiveness was reduced by 75 per cent. It is suggested that the anesthesiologist maintain even greater vigilance over his patient during hypothermia since the usual clinical clues to hypercapnia and hypoxia are lacking.

Halothane (Fluothane) for this study was provided by the Ayerst Company.

References

VENTILATORY RESPONSES TO HYPERCAPNIA AND HYPOXIA


NEUROLEPT ANALGESIA Three patients died immediately after induction of neurolept analgesia. All these patients had received vasomotor paralyzing and peripheral vasodilating drugs prior to operation. The sudden death is explained by the additive effect of vasodilators and dehydrobenzperidol, which is also a vasodilator, causing blood to stagnate in dilated arterial and venous vessels thus interfering with venous return. If possible, antihypertensive drugs should be discontinued four days prior to neuroleptanalgesia. The authors have given up the rapid induction promoted by Henschel and replaced it with a continuous infusion method. No complications have been seen in over 500 patients in whom the latter method was used. (Lawin, P., and others: Three Cardiac Arrests During Induction of Type II Neurolept Analgesia in Hypertensive Patients Treated with Vasodilating Drugs, Der Anaesthesist 15: 19 (Jan.) 1966.)

MYASTHENIA GRAVIS Current evidence suggests that the etiologic of myasthenia gravis may be related to abnormal immune mechanisms because of its frequent association with more clearly defined immunologic disorders. Trimethadione was administered to a patient with myasthenia gravis. This drug, which interferes with the immune state, produces a toxic effect which is clinically indistinguishable from the naturally occurring disease process of myasthenia gravis and may be fatal if the drug is continued. Thus myasthenia gravis may be a rare complication of trimethadione therapy. (Peterson, H. deC.: Association of Trimethadione Therapy and Myasthenia Gravis, New Eng. J. Med. 274: 506 (Mar. 3) 1966.)