The Effects of Anesthetic Agents and Techniques on Canine Cerebral ATP and Lactate Levels

John D. Michenfelder, M.D., Russell A. Van Dyke, Ph.D., Richard A. Theye, M.D.

Cerebral ATP, lactate, and pyruvate were measured in 64 dogs during seven anesthetic circumstances. In the presence of anesthetic agents associated with even twofold differences in cerebral oxygen consumption (CMRO₂), there were no differences in cerebral ATP and lactate levels or lactate–pyruvate ratios. Similar values were observed after induction of hypothermia (30°C). However, in dogs made hypocapnic (Paco₂ = 10 mm Hg), a threefold increase in cerebral lactate content and a significant reduction in cerebral ATP content (5 per cent) were observed. In hypocapnic, anemic dogs (Hb = 5.0 gm/100 ml), a greater reduction in cerebral ATP content (12 per cent) was observed. EEG’s of all dogs were active. The EEG’s of hypocapnic dogs could not be distinguished from those of hypocapnic, anemic dogs. The increases in cerebral lactate content induced by hypoxia were not associated with increased differences between lactate levels in arterial and sagittal sinus blood. (Key words: Cerebral ATP; Cerebral lactate; Cerebral L/P; Anesthetic agents; Anesthetic techniques; Cerebral metabolism.)

It is well established that in both man and dog different anesthetic circumstances are associated with different rates of cerebral oxygen consumption (CMRO₂).1,4 Within the confines of clinically accepted practice, twofold differences in CMRO₂ may be produced by different anesthetics. That concomitant alterations in the high-energy phosphate stores of the brain may occur during anesthesia has not been thoroughly investigated. Previous studies of cerebral energy stores generally have been limited to small laboratory animals, in which the effects of anesthetics on CMRO₂ are largely unknown.

In previous canine studies, we determined the effects of various anesthetics and techniques on CMRO₂. In the present study, cerebral ATP, lactate, and pyruvate were determined during seven anesthetic circumstances. The findings indicate that anesthetic-induced alterations in CMRO₂ are not accompanied by alterations in cerebral ATP and lactate levels. Significant changes in these levels were observed in dogs made hypocapnic (Paco₂ = 10 mm Hg), however, and this effect was exaggerated by the presence of anemia (Hb = 5.0 gm/100 ml).

Material and Methods

Sixty-four unpremedicated, fasting dogs weighing 12 to 16 kg were studied in the prone position. Anesthesia was induced and maintained throughout the surgical preparation with halothane (Fluothane), 1.0 per cent, in nitrogen (60 to 70 per cent) and oxygen. After administration of succinylcholine (30 mg), the trachea was intubated with a cuffed endotracheal tube, and ventilation controlled with a Harvard pump. The percentage of inspired oxygen, respiratory rate, and tidal volume were adjusted as required to maintain the Paco₂ between 100 and 200 mm Hg and Paco₂ at the desired level. Muscle paralysis was maintained by continuous intravenous infusion of succinylcholine (150 mg/hr). Arterial blood pressure was transduced by strain gauge. Normothermia (37.0 ± 0.1°C) was maintained by electrically-heated blankets under the dogs and heat lamps above them. Expired halothane concentration was determined with an infrared analyzer.

The cerebral hemispheres were exposed by bilateral frontoparietal craniotomy, followed by incision and retraction of the dura. Thereafter, the brain was covered with saline-soaked sponges, except during recording of the EEG or biopsy of the brain. A thermistor probe was secured in the parietal epidural space.
EEG recordings were obtained intermittently from the cortical surface.

Anesthetic circumstances previously studied were reproduced in seven groups of dogs prior to biopsy of the brain (table 1). The concentration of halothane required for maintenance of adequate anesthesia during the surgical preparation (0.8 per cent, expired) was adopted as the control circumstance. In two of the groups, halothane concentration was reduced to less than 0.1 per cent, and, in one of these, 70 per cent N₂O, was administered. In the remaining dogs, the control anesthetic circumstances were modified by other maneuvers. In one group, thiopental was administered by continuous intravenous infusion at a rate of 23 mg/kg/hr for two hours. In another group, hypothermia to 30 C was induced by application of ice and alcohol to the body surface. In two groups, profound hypocapnia (Paco₂ = 10 mm Hg) was produced by hyperventilation, and in one of these, hemoglobin concentration was reduced to about 5.0 g/ml by simultaneous arteriotomy and infusion of low-molecular-weight dextran. In all, mean arterial pressures remained above 75 mm Hg, and the blood buffer bases were maintained between 46 and 52 mEq/liter.

When these circumstances were established, the EEG was recorded, and arterial and sagittal sinus blood was sampled for measurement of lactate and pyruvate (omitted in hypothermic dogs). Immediately thereafter, two to six biopsy specimens of brain were obtained from each dog, using a cortical biopsy apparatus similar to that described by Kramer et al., and the dog was sacrificed. The duration of the experiments varied from two and a half hours (control dogs) to five hours (hypothermic dogs).

The cortical biopsy apparatus used provides a core of brain tissue weighing between 200 and 500 mg, which is deposited in liquid nitrogen within 0.5 second after the cortical surface is punctured. Variable amounts of blood are included with the brain biopsy specimens. This is a potential source of error in measuring cerebral ATP, since blood ATP content is approximately a tenth that of brain. For this reason, autologous erythrocytes tagged with ⁵¹Cr (150 μc) were injected prior to each study, and after determination of the radioactivity of the brain biopsy specimens and the blood, the amount of blood in each specimen was calculated. This, along with measurement of blood ATP, permitted correction for this variable. Each biopsy site was separated by 1 to 2 cm of nontraumatized cortex, and biopsy specimens were taken at two-minute intervals, as recommended by Kramer et al. Variability in ATP, lactate, and pyruvate could not be related to sites, sizes, or sequences of brain biopsies.

Each core of tissue was handled in a manner intended to minimize the possibility of thawing and loss of ATP during preparation. After weighing, 2 ml of cold (0 to 4 C) 8 per cent pereloric acid were added and the frozen brain tissue was ground for a minute with a high-speed tissue homogenizer. During grinding, the tissue container was immersed in a dry ice-alcohol slush (−70 C). Thereafter, the homogenate, maintained at a temperature of 0−4 C, was centrifuged, neutralized with potassium hydroxide, buffered, and brought to a volume of 10 ml. Samples of this preparation were taken for determination of ATP, lactate, and pyruvate concentrations. Lactate and pyruvate concentrations in both blood and brain were determined by standard enzymatic methods. Lactate−pyruvate ratios (L/P) and arterial−sagittal sinus blood lactate differences [(A−V) lactate] were calculated.

ATP concentrations were measured by the firefly luminescence method. Fresh standards were prepared daily. To each standard, a 300-mg portion of the dog's brain, which had been maintained at room temperature for more than an hour, was added (ATP content approximately zero). Thereafter, all standards were exposed to the same processes as the frozen brain samples. The light output produced by the ATP-luciferin reaction was measured by a photomultiplier tube system. Peak light output was linear over an ATP concentration range of 0.25 to 2.0 μg/25 μl.

Significances of differences between mean values were tested by Student's t test for unpaired data.
TABLE 1. Anesthetic Circumstances Prior to Brain Biopsy

<table>
<thead>
<tr>
<th>Anesthetic Circumstance</th>
<th>Number of Dogs</th>
<th>Expired</th>
<th>Mean Arterial Pressure (mm Hg)</th>
<th>Epidural Temperature (°C)</th>
<th>Hemoglobin (gm/100 ml)</th>
<th>Pulse (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Halothane, 0.5 per cent</td>
<td>11</td>
<td>0.8</td>
<td>0.0</td>
<td>0</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Halothane, &lt;0.1 per cent</td>
<td>15</td>
<td>&lt;0.1*</td>
<td>0.0</td>
<td>135*</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N₂O₂, 70 per cent</td>
<td>8</td>
<td>&lt;0.1*</td>
<td>0.0</td>
<td>143*</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiopental, 46 mg/kg</td>
<td>14</td>
<td>0.8</td>
<td>0.0</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypothermia, 30 C</td>
<td>5</td>
<td>0.8</td>
<td>0.0</td>
<td>80*</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypocapnia</td>
<td>5</td>
<td>0.8</td>
<td>0.0</td>
<td>104</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypocapnia and anemia</td>
<td>6</td>
<td>0.8</td>
<td>0.0</td>
<td>102</td>
<td>2</td>
</tr>
</tbody>
</table>

* Significantly different from halothane, 0.5 per cent (P < 0.05).

Results

The pertinent experimental conditions in the anesthetic circumstances studied are summarized in Table 1. Significant differences in halothane concentration, epidural temperature, hemoglobin concentration, PₐCO₂, and pH existed only when these variables had been altered intentionally. A reduction in expired halothane concentration to less than 0.1 per cent was accompanied by a significant increase in mean arterial pressure (MABP), a response not modified by the administration of N₂O (70 per cent). Significant reductions in MABP were observed in hypothermic dogs.

Cerebral ATP, lactate, and lactate–pyruvate ratios were not altered by differences in halothane concentration or by the addition of N₂O, thiopental, or hypothermia, despite large differences in the effects of these circumstances on CMRO₂ (Table 2). When the observations were pooled, the mean values (±SE) for cerebral ATP, lactate, and L/P were 2.24 ± 0.03, 2.06 ± 0.20, and 15 ± 2, respectively. Profound hypocapnia produced a small (5 per cent) but significant reduction in cerebral ATP, along with increases in cerebral lactate and cerebral L/P. This degree of hypocapnia did not, in a previous study, alter CMRO₂.

The addition of extreme anemia in hypocapnic dogs produced a 12 per cent decrease in cerebral ATP and a further increase in cerebral L/P. This circumstance had previously been shown to cause a significant decrease in CMRO₂.

In individual dogs, there were no differences between the L/P of arterial and that of sagittal sinus blood; these values were pooled. The L/P of blood was similar to the cerebral L/P in all but the hypocapnic dogs. In these, both lactate and pyruvate levels in the blood increased, whereas in brain, lactate increased to a greater degree than pyruvate. With the addition of anemia, both the L/P of blood and the cerebral L/P were significantly elevated, suggesting whole-body as well as cerebral hypoxia. Despite the threefold increases in cerebral lactate in hypocapnic dogs, (A-V) lactate values were similar to those in normocapnic dogs, not different from zero.

In all dogs, EEG's were active prior to biopsy of the brain. The least activity was observed in the dogs receiving thiopental. In these, the EEG's were characterized by a burst-suppressive pattern. The EEG's in the two groups of hypocapnic dogs had similar high-amplitude, low-frequency patterns.

Discussion

It is commonly stated in the neurochemistry literature that anesthetics increase the high-energy phosphate stores (ATP and phosphocreatine) of brain. This assumption is based largely on studies of small animals anesthetized with barbiturates. McIlwain concluded that an anesthetic-induced reduction in cerebral respiration decreases the utilization of energy stores to a greater degree than synthesis is diminished; as a result, ATP and phosphocreatine accumulate. This has been disputed by Minard and Davis, who reported no effect of anesthetics on cerebral energy stores in the rat. In the present study,
anesthetic circumstances known to have widely divergent effects on CMRO$_2$ were examined. In the absence of hypoxia, no significant differences in cerebral ATP contents were observed. We conclude that anesthetic-induced alterations in cerebral respiration are balanced by quantitatively similar alterations in the rates of ATP synthesis and ATP utilization.

Discrepancies in the reported effects of anesthetics on cerebral energy stores probably relate to differences in methodology, as well as species. Recovery of ATP and phosphocreatine from tissue is complicated by the extreme lability of these substances. Minor differences in methods of tissue collecting, freezing, and preparing may be critical. Most investigations of cerebral ATP have been done in rats or mice. The brains of these animals generally are frozen in liquid nitrogen, either by immersion of the intact heads or by pouring liquid nitrogen over the exposed brains. A time lapse necessarily occurs between freezing of the brain surface and core. This may be between 9 and 80 seconds, depending on the size of the brain and the freezing method used.$^{15-17}$ If during this time the unfrozen brain becomes hypoxic, depletion in ATP and phosphocreatine would occur. Minard and Davis$^{16}$ reported that the rates of depletion of these substances after decapitation of anesthetized rats were significantly less than those observed in nonanesthetized rats. They suggested that these reduced rates of depletion were either a direct effect of the anesthetic or secondary to reductions in body temperature of anesthetized animals. In either case, such an effect, after a brief period of hypoxia, would result in concentrations of ATP and phosphocreatine that were relatively greater in anesthetized than in nonanesthetized animals. Another potential source of error relates to possible differences in intracerebral blood volume at the time of freezing. Such variability would be particularly likely to occur in anesthetized animals secondary to changes in blood gases, arterial blood pressure, or the anesthetic itself. Because the ATP content of the blood is approximately a tenth that of brain, failure to correct for differences in blood volume could introduce significant error.

Differences in species also might account for discrepancies in reported observations. Such a difference is suggested by the different rates of ATP depletion observed in dogs and rats during anoxia. Kramer$^{6}$ reported, in anesthetized dogs, a gradual decline in ATP to approximately 20 per cent of normal after six minutes of anoxia. Lowry$^{6}$ studying nonanesthetized adult rats, observed a similar diminution within the first minute of anoxia. It seems unlikely that such remarkable differences can be accounted for solely by the presence or absence of anesthetics.

The methods used in the present study offer several advantages. The use of large animals permits careful control of all of the important variables known to affect cerebral metabolism and CBF. Multiple brain samples can be obtained from each animal, as opposed to the availability of only one sample in the small

<table>
<thead>
<tr>
<th>Anesthetic Circumstance</th>
<th>Cerebral ATP (µmol/gm) Mean SE</th>
<th>Cerebral Lactate (µmol/gm) Mean SE</th>
<th>Cerebral L/P Mean SE</th>
<th>CMRO$_2$ (µmol/100 gm/min) Mean SE</th>
<th>(A-V) Lactate (µmol/l) Mean SE</th>
<th>Blood L/P Mean SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane, 0.5 per cent</td>
<td>2.26 0.03</td>
<td>2.20 0.27</td>
<td>13 1</td>
<td>4.65 0.16</td>
<td>0.00 0.10</td>
<td>13 1</td>
</tr>
<tr>
<td>Halothane, &lt;0.1 per cent</td>
<td>2.30 0.03</td>
<td>1.83 0.18</td>
<td>12 1</td>
<td>5.53 0.26</td>
<td>-0.02 0.04</td>
<td>13 1</td>
</tr>
<tr>
<td>N$_2$O, 70 per cent</td>
<td>2.33 0.05</td>
<td>2.63 0.19</td>
<td>15 4</td>
<td>5.80 0.17</td>
<td>0.01 0.05</td>
<td>12 1</td>
</tr>
<tr>
<td>Thiopental, 46 mg/kg</td>
<td>2.21 0.02</td>
<td>1.75 0.17</td>
<td>17 4</td>
<td>2.80 0.16</td>
<td>0.00 0.03</td>
<td>10 1</td>
</tr>
<tr>
<td>Hypothermia, 30 C</td>
<td>2.29 0.05</td>
<td>2.35 0.20</td>
<td>15 4</td>
<td>2.80 0.16</td>
<td>0.00 0.03</td>
<td>10 1</td>
</tr>
<tr>
<td>Hypoexcipia</td>
<td>2.14 0.01</td>
<td>6.23 0.47</td>
<td>23 3</td>
<td>4.19 0.28</td>
<td>-0.03 0.10</td>
<td>15 1</td>
</tr>
<tr>
<td>Hypoexcipia and anemia</td>
<td>1.88 0.06</td>
<td>6.26 0.61</td>
<td>30 3</td>
<td>3.99 0.23</td>
<td>0.03 0.13</td>
<td>21 2</td>
</tr>
</tbody>
</table>

* Data from previous studies.$^{1,4-8}$
† Significantly different from halothane, 0.5 per cent ($P < 0.05$).
animal. The method of biopsying brain results in freezing of the sample in less than a second. Finally, these methods permit study of the same species, the same anesthetic circumstances, and the same portion of the brain (cerebral hemispheres) previously investigated in our CMRO₂ studies.

The pooled mean values for cerebral ATP (2.24 ± 0.03), lactate (2.06 ± 0.20), and L/P (15 ± 2) observed in the present study are well within the range of values reported by others for various species in the presence of various anesthetics (table 3).

Our observations are in agreement with those of Minard and Davis, in that cerebral ATP contents were constant in the presence of various anesthetics. This is contrary to the observations of Granholm et al.,† who reported significant differences in cerebral ATP and lactate levels and in cerebral L/P between different agents and different doses of the same agent. In that study, body temperature apparently was not controlled, nor was correction made for variations in intracerebral blood content. The stability of cerebral ATP, lactate, and pyruvate that we observed during anesthetic circumstances associated with different CMRO₂ effects is not surprising. All of these circumstances (in the absence of hypocapnia) are known to be free from cerebral hypoxia, reversible, and clinically safe. That the ATP stores of the brain are unaffected by anesthetic circumstances suggests a potential cerebral protective effect for those agents which significantly reduce CMRO₂. Evidence for a cerebral protective effect by some anesthetics in the presence of hypoxia has been reported. Presumably, such an effect would also exist in the presence of anoxia.

Modification of the control circumstances by profound hypocapnia (Paco₂ = 10 mm Hg) does affect cerebral ATP and lactate levels and cerebral L/P. Previous studies in man and in the dog suggested that this level of hypocapnia produces alterations in cerebral metabolism secondary to hypoxia. Evidence for this has consisted primarily of an increase in cerebral glucose consumption and, in turn,

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Anesthetic</th>
<th>Cerebral ATP (μmol/gm)</th>
<th>Cerebral Lactate (μmol/gm)</th>
<th>Cerebral L/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer et al.⁹</td>
<td>Dog</td>
<td>Pentobarbital, 25 mg/kg</td>
<td>2.42 ± 0.16*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lowry et al.¹⁵</td>
<td>Mouse (10 days old)</td>
<td>Phenobarbital, 150 mg/kg</td>
<td>2.58†</td>
<td>0.77†</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Mouse (10 days old)</td>
<td>None</td>
<td>2.74</td>
<td>1.63</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Mouse (adult)</td>
<td>None</td>
<td>2.36</td>
<td>2.26</td>
<td>—</td>
</tr>
<tr>
<td>Minard and Davis¹⁴</td>
<td>Rat</td>
<td>None, Chlorpromazine, 10 mg/kg</td>
<td>2.65 ± 0.06</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ether (?)</td>
<td>2.04</td>
<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>Phenobarbital, 150 mg/kg</td>
<td>2.08</td>
<td>—</td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>2.13</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Thurston and McDougal¹⁹</td>
<td>Mouse (newborn)</td>
<td>None</td>
<td>2.25 ± 0.16</td>
<td>2.7 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td>Granholm et al.¹⁵</td>
<td>Rat</td>
<td>N₂O, 70 per cent</td>
<td>2.34 ± 0.06</td>
<td>1.46 ± 0.09</td>
<td>15.0 ± 0.6†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenobarbital, 175-200 mg/kg</td>
<td>2.43 ± 0.02</td>
<td>0.86 ± 0.03</td>
<td>11.3 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>Phenobarbital, 150 mg/kg</td>
<td>2.54 ± 0.03</td>
<td>1.12 ± 0.13</td>
<td>17.1 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Cat</td>
<td>Phenobarbital, 100 mg/kg</td>
<td>2.13 ± 0.04</td>
<td>0.71 ± 0.07</td>
<td>11.0 ± 0.4</td>
</tr>
</tbody>
</table>

* Mean ± SE.
† Mean.
a decrease in the calculated oxygen–glucose index (OCl) and an increase in the lactate–glucose index (LCl). Alexander et al.\textsuperscript{21} also reported a small (10 per cent), but not significant ($P = 0.08$), decrease in $\text{CMR}_{\text{O}}$ during hypoxemia; this was not observed in the dog.\textsuperscript{8} These observations, although suggestive of hypoxia, were not conclusive, since it is known from in vitro studies that alkalosis alone can increase cerebral glucose consumption.\textsuperscript{22} The current observation of a significant reduction in cerebral ATP supports the conclusion that profound hypoxemia does cause alterations in cerebral metabolism secondary to hypoxia. The significant increases in cerebral lactate and L/P during hypoxemia provide further evidence in support of this conclusion, and have been observed by others.\textsuperscript{23, 24} The addition of extreme anemia to hypoxemia in dogs exaggerated the hypoxic effects of hypoxemia, as evidenced by further reduction in the ATP content and increase in the L/P. In this circumstance, we previously had observed a significant reduction in $\text{CMR}_{\text{O}}$, considered to be secondary to hypoxia.\textsuperscript{6}

Significant A-V differences in lactate did not occur in any of the dogs studied, inconsistent with the common assumption that 5 to 15 per cent of the glucose consumed by the brain is anaerobically metabolized to lactate.\textsuperscript{25, 26} This assumption has been disputed by Scheinberg et al.,\textsuperscript{27} who could find no evidence in blood lactate measurements of lactate production by the normal brain. However, it is clear from our experiments on hypoxemic dogs that lactate levels do not necessarily reflect cerebral lactate production. This has been observed previously by Plum and Posner\textsuperscript{23} and explained by the presence of a significant brain–blood barrier for lactate. In their study, changes in cerebral lactate production were most clearly reflected by changes in lactate concentration in cerebrospinal fluid.

The reduction of 12 per cent in cerebral ATP that occurred in dogs made hypoxemic and anemic was not associated with gross differences in the EEG, compared with dogs made hypoxemic only. This is contrary to the observations of Kramer et al.,\textsuperscript{9} who found that in hypothermic dogs reductions of 10 per cent in cerebral ATP were always associated with flat EEG's. They postulated that this might represent a critical ATP level in regard to the electric activity of the brain. The presence of an active EEG must be dependent on various factors, of which ATP may be only one. If so, it is unlikely that a single ATP level critical for all circumstances exists.

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Drugs

ANTIBIOTICS AND PROTEIN SYNTHESIS. Most antibiotics, with the ex-
ception of those that act on cell wall assembly, exert their bacteriostatic and bac-
tericidal effects by virtue of their inhibitory effects on protein synthesis. Protein
synthesis represents the end-result of three processes: 1) deoxyribonucleic acid
(DNA) synthesis, or replication; 2) DNA-dependent ribonucleic acid (RNA)
synthesis, or transcription; 3) RNA-dependent protein synthesis or translation. Anti-
biotics which inhibit any of these processes will inhibit protein synthesis, but those
that inhibit primarily translation are the most effective clinically. It has been as-
sumed that agents in this category inhibit bacterial protein synthesis without pro-
ducing similar effects on host protein. However, in the past ten years it has be-
come increasingly apparent that several antibiotics may inhibit mammalian systems
and therefore threaten the host as well as the invading bacteria. Mammalian cells
that are replicating rapidly or undergoing new protein synthesis are particularly
susceptible to inhibition. Chloramphenicol, tetracyclines, the aminoglycoside family
(e.g., streptomycin, oleandomycin), and other generic antibiotic types have been
implicated in this regard. (Beard, N. S., Jr., Armentrout, S. A., and Weisberger,
21: 213 (Sept.) 1969.) Abstractor's Comment: Of special interest to anesthesi-
ologists is the observations that antibiotic-induced inhibition of protein synthesis
has been shown to prolong sleep time from barbiturates; to delay recovery from con-
duction blockade produced by local anesthetics, and perhaps to shorten induction
time and prolong recovery time following exposure to halothane.