A THEORY OF GASEOUS ANESTHETICS*

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In the course of an investigation of gas hydrates at low temperatures and their occurrence in the solar system,1 it was noticed that many of the gases which form hydrates, such as ethylene, nitrous oxide, chloroform, and xenon, are also gaseous anesthetics.2 A comparison of the pressure of anesthetic necessary to maintain a person in a given stage of anesthesia and the dissociation pressure of the hydrate at 0°C shows that there is indeed a correlation. The data are shown in Table 1. The ratio of anesthetic pressure to hydrate dissociation pressure is in the range 0.1 to 0.5, except for the low value of carbon dioxide and the high values of sulfur hexafluoride and xenon. The ratios are about the same for both Structure I hydrates (Gas·6 to 10 H2O) and the Structure II hydrates (Gas·17 H2O).

Taking into account the uncertainties of the data, the correlation can be considered good, with some of the agreement probably being fortuitous. This correlation is as good as the correlations obtained with the Meyer-Overton lipid theory of anesthesia.5

The gas hydrates: The gas hydrates are clathrate compounds of a gas engaged in a distorted ice matrix (for reviews, see refs. 3 and 17). These crystalline compounds occur in two forms, and the structures have been determined.12, 17–20. Structure I has a cubic unit cell 12.0 Å on edge containing 46 water molecules and 8 cavities. The two smaller cavities are pentagonal dodecahedra each formed by an array of 20 water molecules giving a cavity of 3.95 Å which can encage molecules with diameters of 5.1 Å or less. The six larger cavities are tetrakaidecahedra (with two opposite hexagonal faces and 12 pentagonal faces) each formed by an array of 24 water molecules, giving a cavity of 4.3 Å radius which can encage molecules with diameters of 5.8 Å or less.

Structure II hydrates have a cubic unit cell of 17.4 Å on edge containing 136 water molecules and 24 cavities. The sixteen smaller cavities are distorted pentagonal dodecahedra each formed by an array of 20 water molecules giving a cavity of 3.91 Å radius which can encage molecules with diameters of 5.0 Å or less. The eight larger cavities are hexadecahedra each formed by an array of 28 water molecules giving a cavity 4.73 Å radius which can encage molecules with diameters of 6.7 Å or less.

Gases which form hydrates but are not anesthetics: There are a number of gases,
TABLE 1

COMPARISON OF THE GAS REQUIRED FOR SURGICAL ANESTHESIA4 AND THE DISSOCIATION PRESSURE OF THE HYDRATE AT 0°C

<table>
<thead>
<tr>
<th>Gas</th>
<th>Pressure (atm) of anesthesia</th>
<th>Dissociation pressure (atm) of hydrate at 0°C</th>
<th>( P_{\text{anesthesia}} / P_{\text{hydrate}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen</td>
<td>20</td>
<td>160</td>
<td>15</td>
</tr>
<tr>
<td>Argon</td>
<td>20</td>
<td>95</td>
<td>15</td>
</tr>
<tr>
<td>Krypton</td>
<td>2.9</td>
<td>14.5</td>
<td>15</td>
</tr>
<tr>
<td>Xenon</td>
<td>0.85</td>
<td>1.2</td>
<td>15</td>
</tr>
<tr>
<td>Methane</td>
<td>4.6</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Ethane</td>
<td>1.3</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Ethylene</td>
<td>0.80</td>
<td>5.54</td>
<td>15</td>
</tr>
<tr>
<td>Acetylene</td>
<td>0.70</td>
<td>5.7</td>
<td>15</td>
</tr>
<tr>
<td>Cyclopropane</td>
<td>0.15</td>
<td>0.63</td>
<td>15</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>0.90</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>0.25</td>
<td>12.5</td>
<td>15</td>
</tr>
<tr>
<td>Methyl fluoride</td>
<td>0.14</td>
<td>2.1</td>
<td>15</td>
</tr>
<tr>
<td>Methyl chloride</td>
<td>0.14</td>
<td>0.41</td>
<td>15</td>
</tr>
<tr>
<td>( \text{CH}_3\text{CHF}_2 )</td>
<td>0.45</td>
<td>0.82</td>
<td>15</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.015</td>
<td>0.062</td>
<td>15</td>
</tr>
<tr>
<td>Ethyl chloride</td>
<td>0.04</td>
<td>0.27</td>
<td>15</td>
</tr>
<tr>
<td>Propane</td>
<td>0.9</td>
<td>1.74</td>
<td>15</td>
</tr>
<tr>
<td>Propene</td>
<td>0.4</td>
<td>4.3</td>
<td>15</td>
</tr>
<tr>
<td>Sulfur hexafluoride</td>
<td>3.0</td>
<td>1.0</td>
<td>15</td>
</tr>
<tr>
<td>Methyl iodide</td>
<td>0.07</td>
<td>0.097</td>
<td>15</td>
</tr>
<tr>
<td>Ethyl bromide</td>
<td>0.04</td>
<td>0.20</td>
<td>15</td>
</tr>
<tr>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>0.050</td>
<td>0.15</td>
<td>15</td>
</tr>
<tr>
<td>CF₂Cl₂</td>
<td>0.6</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>CFC₃</td>
<td>0.15</td>
<td>0.54</td>
<td>15</td>
</tr>
<tr>
<td>( \text{CH}_2\text{CHCl}_2 )</td>
<td>0.026</td>
<td>0.072</td>
<td>15</td>
</tr>
</tbody>
</table>

such as \( \text{H}_2\text{S}, \text{SO}_2, \text{Cl}_2, \text{O}_2, \text{CHCl}_2\text{F}, \text{C}_2\text{H}_4\text{F}, \text{etc.} \), which form hydrates, but are not known to have anesthetic properties. These gases exhibit acute toxic reactions at pressures lower than those probably necessary for narcosis and are therefore omitted from the table.

Gases which have no narcotic properties: Helium, hydrogen, and probably neon have no anesthetic effect, and these gases do not form hydrates.

Local anesthetics: The mechanism of action of local anesthetics which are tertiary or quaternary amines is almost certainly different from gaseous anesthetics, and therefore will not be discussed here.

The Formation of Hydrates during Anesthesia.—In order to determine if crystalline hydrates could be formed in the body during the administration of an anesthetic, it is necessary to extrapolate the dissociation pressures to 37°C, since the pressures given in the table refer to 0°C.

The dissociation pressure of a hydrate as a function of temperature is given by the integrated Clausius-Clapeyron equation

\[
\log \frac{P_1}{P_0} = \frac{\Delta H}{2.3R} \left( \frac{1}{T_0} - \frac{1}{T_1} \right)
\]

where \( \Delta H \) is the enthalpy of the reaction of 1 mole of gas with \( n \) moles of liquid water to form a solid hydrate \( G \cdot n\text{H}_2\text{O} \), \( R \) is the gas constant and the \( T \)'s are the absolute temperatures.

For hydrates of Structure I, the \( \Delta H \)'s are about 16 kcal/mole, giving \( P_37/P_0 = 33 \). For hydrates of Structure II, the \( \Delta H \)'s are about 31 kcal/mole, giving \( P_37/P_0 = 915 \).
These figures refer to the reaction of the gas with pure water to give a hydrate, and therefore must be corrected for the effects of salts in the interstitial and intracellular fluids. Taking the salt concentration as 0.32 osmolar and omitting the effect of the dissolved anesthetic, the activity of water in interstitial fluid is lowered by 0.58 per cent. The increase in gas pressure needed to form a hydrate due to the lowering of the activity of the water is given by the equation

\[ a_G = a_{H_2O}^{-n} \]  

(2)

where \( a_G \) is the activity of the gas relative to the dissociation pressure of the hydrate with pure water, \( a_{H_2O} \) is the activity of water in the interstitial fluid relative to pure water, \( n \) is the ratio of water to gas in the crystalline hydrate (about 7 for Structure I hydrates and 17 for Structure II hydrates). This raises the dissociation pressure by a factor of 1.04 for Structure I hydrates, and 1.10 for Structure II hydrates.

Combining these factors, the pressure to form, for example, \( N_2O \) hydrate in interstitial fluid is 343 atm, while the observed pressure for anesthesia is 0.90 atm. This is a free energy unfavorable by \( \Delta G = RT\ln\left[P_{hydrate}/P_{anesthesia}\right] = 3.6 \) kcal/mole of gas or \( \Delta G = 0.51 \) kcal/mole of water.

For a Structure II hydrate, for example \( CHCl_3 \), the pressure to form a hydrate at 37°C in interstitial fluid is 63 atm, while the observed pressure for anesthesia is 0.015 atm. This gives a free energy unfavorable by 5.1 kcal/mole of gas or 0.30 kcal/mole of water.

These pressures (fugacities) of \( N_2O \) and \( CHCl_3 \) cannot be obtained at 37°C since these gases liquefy at much lower pressures, and in any case the hydrates of \( N_2O \) and \( CHCl_3 \) are not stable above 10°C and 1.6°C, respectively.

These hydrates could be stable at 37°C if the activity of water could be increased, equation (2). This may be possible in isolated systems where small particles of ice or water can be in a metastable condition. However, since the cells are in osmotic equilibrium with the interstitial fluid, the activity of water is the same throughout the body. Therefore, it would appear to be impossible that crystalline hydrates could form during anesthesia. In addition, hydrates are formed at a definite pressure, below which the hydrate is unstable, but anesthetics exert a continuously increasing effect as the pressure is raised.

If the correlation of anesthetic potency and hydrate dissociation pressures is assumed to be more than accidental, then we must examine the interactions of gases in aqueous solution, for which the ability to form hydrates is but one expression.

**Gases in Aqueous Solution.**—It has been pointed out by several investigators\(^{21}\) that the low solubilities, large entropies of solution, and large partial molal heat capacities of nonpolar gases in water can be interpreted to mean that the water surrounding a dissolved gas molecule is in a more highly ordered state than the water in bulk solution. This more highly ordered water is sometimes referred to as "iceberg."

Most of the theories of the structure of water assume that ice-like configurations are present in liquid water.\(^{22}\) Pauling has proposed a model of liquid water which is a Structure I hydrate with the cavities occupied by water molecules instead of gas molecules.\(^{23}\) Although none of these theories has been accepted as the correct description of liquid water, it seems likely that ice-like clusters, probably of several
types, do exist in liquid water. These "icebergs" would be in a dynamic state, constantly being formed and broken down.

It has also been proposed that some of the water in proteins is ice-like, and that these "icebergs" play a significant role in the properties of these polymers.24, 25

We will assume that these "icebergs" are present in liquid water, and that the gas molecule is also surrounded by "icebergs."

Not all the gas molecules dissolved in water are surrounded by "icebergs." A fraction of the gas molecules occupy quasi-lattice sites in the water, and this fraction depends on the gas dissolved. It is high for helium and low for xenon. An estimate of the "iceberg" present might be obtained from the partial molal entropies of solution or partial molal heat capacities, but these quantities are not accurately known or the data are not available. Therefore, we shall examine this problem from the standpoint of the binding of a gas molecule in a cavity in liquid water, in particular in a water cavity near some surface. Whether this surface is the surface of a membrane, the "surface" of a protein, mucopolysaccharide or other polymer will not alter the discussion. This treatment would also apply to the "icebergs" around gas molecules in bulk water, and this might permit the calculation of solubilities and partial molal entropies of solution for nonpolar gases.

We shall attempt to calculate the fraction of the surface covered by water which is in a more highly ordered (or icelike) state than in the liquid water. This cumbersome expression will be abbreviated "ice cover."

It has been shown that the dissociation pressure of a clathrate with a single type of cavity in terms of the fraction of cavities occupied and the binding energy in the cavity is given by the equation26

\[ P_A = \frac{y}{1 - y} \frac{kT}{2\pi a^2y} \exp \left[ \frac{w(0)}{kT} \right] \]  

(3)

where \( P_A \) is the pressure of the gas, \( y \) is the fraction of cavities (or sites) occupied by the gas molecules, \( k \) is Boltzmann's constant and \( T \) is the absolute temperature. The quantity \( w(0) \) is the energy of binding at the center of a preformed cavity (or site) and \( 2\pi a^2y \) is the free volume of the molecule in the cavity. These latter two quantities have been calculated with some success by means of the Lennard-Jones, Devonshire theory.3, 27 This equation is analogous to a Langmuir adsorption, in which the bound molecules are adsorbed on independent sites and there are no interactions between the adsorbed molecules.28 Written in molar quantities this becomes,

\[ P_A = \frac{y}{1 - y} \frac{RT}{V_f} \exp \left( -\frac{\Delta E}{RT} \right) \]  

(3a)

where \( V_f \) is the free volume per mole and \( \Delta E \) is the energy of vaporization from the cavities.

We will assume that the surface under consideration has three types of water. A fraction \( X_w \) consists of "liquid water" which has no icelike structure. The second fraction \( X_I \) is icelike or "iceberg" water. These "icebergs" will be assumed to contain a cavity that can encage a gas molecule but the cavity is empty. The third fraction of the total water \( X_A \) consists of "icebergs" which have gas molecules encaged in them.
The ratio of "iceberg" water to liquid water is given by

\[ \frac{X_I}{X_W} = \exp \left( -\frac{\Delta G_I}{RT} \right) \]  \tag{4}

where \( \Delta G_I \) is the free energy to form a mole of these cavities from liquid water. \( \Delta G_I \) is temperature dependent in a manner to make \( X_I \) greater at lower temperature. The number of empty "icebergs" does not change appreciably when dissolved gas molecules are present. When some of the empty "icebergs" become filled with gas molecules, sufficient "liquid water" is converted to "iceberg" to maintain the ratio given by equation (4).

We have from the definition of \( y \)

\[ \frac{X_A}{X_I} = \frac{y}{1 - y} \]  \tag{5}

Combining these two equations gives the ratio of surface covered with gas filled cavities to surface covered with liquid water

\[ \frac{X_A}{X_W} = \exp \left( -\frac{\Delta G}{RT} \right) \frac{y}{(1 - y)} \]  \tag{6}

Combining with equation (3a) for \( \frac{y}{(1 - y)} \) gives

\[ \frac{X_A}{X_W} = P_A \frac{V_f}{RT} \exp \left( \frac{\Delta E}{RT} \right) \exp \left( -\frac{\Delta G_I}{RT} \right) \]  \tag{7}

or

\[ P_A = \frac{X_A}{X_W} \frac{RT}{V_f} \exp \left( -\frac{\Delta E}{RT} \right) \exp \left( -\frac{\Delta G_I}{RT} \right) \]  \tag{7a}

This equation states that at a given temperature the "ice cover"/water ratio at a surface in the different stages of anesthesia is proportional to the pressure of the anesthetic. The term \( (RT/V_f) \exp \left( -\frac{\Delta E}{RT} \right) \) is proportional to the dissociation pressure of the hydrate along the ice-hydrate-gas equilibrium extrapolated to 37°C, assuming that the cavities in the "iceberg" are the same as in the hydrate. In order to have a correlation of anesthetic pressures with hydrate dissociation pressures at 0°C, the \( \Delta G_I \) term would have to compensate for the variations in \( \Delta E \). The \( \Delta E \)'s vary from 3 to 8 kcal for both hydrate structures. The larger \( \Delta E \)'s are associated with the larger molecules in most cases, but the larger molecule will only fit into a larger cavity. This larger cavity will have a greater \( \Delta G_I \) of formation than a smaller cavity, and the quantity \( \Delta E - \Delta G_I \) will remain approximately constant for molecules of both hydrate structures.29 Therefore, if we assume this model of anesthetic activity to be correct, the correlation of anesthetic potency at 37°C and the hydrate dissociation pressures at 0°C can be understood.

Anesthetics which do not form hydrates: There are many gases which have anesthetic properties but, in so far as is known, do not form hydrates. The most notable of these is diethyl ether. The list also includes hydrocarbons higher than propane, aromatic hydrocarbons, various ethers and halogenated derivatives of these compounds.

These higher molecular weight anesthetics are too large in size to enter the cavities of Structures I or II. It is as likely that these larger molecules are surrounded by "icebergs" in aqueous solution as it is for gases which form hydrates, since these larger molecules also have large entropies of solution and large partial molal heat capacities in solution. Equation (7) would apply to these gases for
which hydrates are not known. If good estimates of $\Delta E$, $\Delta G$, and $V_f$ could be made, the correlation in Table 1 of anesthetic potency and "ice-cover" could be extended to include these larger molecules.

This argument would be strengthened if hydrates of these larger molecules could be shown to exist, and attempts are being made in this laboratory to prepare them.

Hydrogen bonding anesthetics: Alcohol, esters, ketones and aldehydes have anesthetic properties, and it seems likely that these compounds would increase the "ice cover" of membranes. In the case of acetone the hydrate is known (Structure II). It is not likely that the "ice cover" formed by these compounds could be estimated by assuming that they are simply engaged in an empty "iceberg" cavity. The effects of hydrogen bonding and dipole interactions with the water would have to be taken into account. Therefore, these anesthetics will not be examined here even though they may, in the final analysis, act in the same way as non-hydrogen bonding anesthetics.

The Temperature Effect of Anesthesia.—It would be reasonable to assume that an "iceberg" without a gas molecule in it ($X_i$) would have the same effect as an "iceberg" containing a gas molecule ($X_A$), with the role of the anesthetic gas being to increase the total amount of "ice cover." This would allow an explanation of the anesthetic effect of hypothermia in the absence of an anesthetic gas. Equation (7) neglects the contribution of $X_i$ to the anesthetic effect, but $X_i$ which is present in any case, subtracts out and allows intercomparisons of different anesthetics as long as the temperature is held constant.

We can include the effect of $X_i$ by taking the total "ice cover," $X_A + X_i$, as the index of anesthetic activity. This gives

$$\frac{X_A + X_I}{X_w} = \exp\left(-\frac{\Delta G_i}{RT}\right) \left[\frac{P_A V_f}{RT} \exp\left(\frac{\Delta E}{RT}\right) + 1\right]$$

Equation (8)

Therefore, if we assume that equal "ice covers" give equal degrees of anesthesia, then the temperature and anesthetic pressures required to attain a given stage of anesthesia are interrelated by this equation.

We have assumed a single type of cavity, but it would be likely that several types of cavities could surround a gas molecule, and that $X_i$ consists of several types of ice-like structures. We can allow for the different types of cavities by summing over the $i$ types of cavities to give

$$\frac{X_A + X_I}{X_w} = \sum_i \exp\left(-\frac{\Delta G_i}{RT}\right) \left[\frac{P_A V_f}{RT} \exp\left(\frac{\Delta E_i}{RT}\right) + 1\right]$$

Equation (9)

There have been to the writer's knowledge no careful studies of the change of the pressure of an anesthetic needed when the temperature of the patient is below or above 37°. Any temperature effect of anesthesia is, of course, complicated by temperature effects on nerve activity and metabolism. This point could be studied by comparing equations (8) or (9) with experimental data, using reasonable values of $\Delta E$ and $\Delta G$. The temperature range available for the investigation with cold blooded animals might permit the evaluation of the (average) constants of equation (9).

It is of interest to consider whether the anesthesia produced by hypothermia is a carbon dioxide anesthesia, an effect on the water, or another effect. Carbon
dioxide anesthesia is attained at 0.25 atm at 37°C, and using \( \Delta H = 16 \) kcal in equation (1) for the extrapolation, carbon dioxide anesthesia would be attained with 0.14 atm at 30°C, which is the temperature for anesthesia by hypothermia. The partial pressure of CO₂ in arterial blood is 0.047 atm at 37°C but is lowered to 0.026 atm during hypothermia.³¹ Therefore, on the basis of this extrapolation, it would appear that the normal carbon dioxide of the blood does not contribute to the anesthesia during hypothermia. This conclusion could be tested by determining the temperature required for anesthesia when the patient is in compensated metabolic alkalosis (high CO₂) and compensated metabolic acidosis (low CO₂).

**Mixtures of Anesthetics.**—If we assume that the sites in which an anesthetic is adsorbed are independent, then it follows that the “ice cover” will be the sum of the effects of each anesthetic. This can be expressed by the equation:

\[
\sum_i P_i/P_i^0 = 1
\]

where \( P_i^0 \) is the pressure of the \( i \)th gas which will produce a given stage of anesthesia when used alone, and \( P_i \) is the partial pressure of this gas in the mixture. Clinical practice of using mixtures of gaseous anesthetics approximates this equation, and this relationship is in accord with the quantitative data for N₂O and CO₂ mixtures.³² These gases both form Structure I hydrates. If the sites were not independent, the effects would still be additive, because both types of molecules can be interchanged in the same cavity.

In mixtures of anesthetics of different size, such as chloroform and cyclopropane, the cyclopropane can enter the cavity occupied by the chloroform, but not the reverse. Therefore, if the sites were not independent, in that the iceberg around the chloroform extended a sufficient distance to form an empty cavity of smaller size, then the cyclopropane would stabilize the chloroform “iceberg” in a non-additive manner. This effect is shown by the stabilization of Structure II hydrates by small molecules which occupy the smaller holes of the Structure II lattice, forming double hydrates (for example, CHCl₃·2H₂S·17H₂O instead of CHCl₃·17H₂O when no H₂S is present). The question whether the sites are independent or not can be easily tested experimentally.

**The Lipid Theory of Narcosis.**—The Meyer-Overton theory of narcosis states that anesthetics are lipid soluble gases, the index of anesthetic potency being the oil/water partition coefficient times the solubility in water. Ferguson³³ and Brink and Posternak³⁴ have used the activity of the anesthetic gas relative to the liquid to correlate anesthetic activity. This choice of standard state, which is arbitrary, implies that equal degrees of anesthesia are produced when equal mole fractions (or volume fractions) of anesthetic are present in the lipid parts of a membrane or other structure which are lipid in character. This treatment has been extended by Mullins⁵ to take into account the more advanced ideas of solution theory.

This correlation of the chemical activity of the anesthetic and its potency can be considered as rather good. There can also be no question that anesthetics enter the lipid membranes. The problem is where do the anesthetics exert their effect. Correlations of anesthetic activity do not answer this question, especially if several different properties of the anesthetic give about equally good correlations.

**The Mechanism of Action of Anesthetics.**—There are many hypotheses of the
mechanism of narcosis that could be proposed in the light of this theory. It is possible that the "ice cover" lowers the conductance, "stiffens up" the lipid membrane, "plugs up" the pores of the membrane, etc. There are also several hypotheses which do not involve mechanical obstructions and which are more accessible to experimental test.

Narcotic agents raise the threshold for conduction along the nerve, and the threshold would be increased by an increase in the capacity of the membrane and associated aqueous double layer. It is possible that an "ice cover" could increase this capacity. At the interface between mercury and aqueous salts, there is an anomalous increase in the differential capacity between the mercury and the outer Helmholtz plane. The anomalous capacity is present when the mercury has a positive surface charge. An explanation offered for this effect is that the water near the mercury is "ice-like." It is interesting to note that this anomalous capacity is markedly increased in the presence of n-heptyl alcohol, which is also a narcotic.

This hypothesis could be tested by measuring the changes in capacitance in the presence of different gaseous anesthetics at the nodes of Ranvier or at unmyelinated nerves. Although the mercury-aqueous salt interface is not a model for a nerve, this system permits the study of the effect of anesthetics on the "ice cover" and the resulting anomalous capacity without the complications due to lipid solubility and changes in permeability and voltage.

It is possible that the anesthetic exerts its effect on the mechanism of permeability change during conduction. In Nachmansohn's theory, this effect would be on acetylcholine esterase, the receptor protein or the storage protein. The effect of anesthetics on the binding constants or enzyme activity could be measured in vitro.

From general considerations, it is apparent that the major effect of gaseous anesthetics is on transmission at synapses (including neurons and the neuromuscular junction).

It has been demonstrated in vitro that the sympathetic ganglion is more sensitive to a given level of anesthetic than a node of Ranvier, although the effect is similar. A capacitance change in the membrane is likely to exhibit a greater overall influence at a synapse than at a nerve, because the presynaptic membrane and postsynaptic membrane form in a sense a condenser in themselves. The relative influence of the capacitance change would depend on the details of the interlocking of the two membranes. The "ice cover" produced by anesthetics could also affect the binding, hydrolysis and diffusion of neurohumoral transmitters.

Summary.—There is a good correlation between the pressure of a gaseous anesthetic required for surgical anesthesia and the dissociation pressure of the corresponding gas hydrate at 0°C. However, it is shown that a gas hydrate will not form in the body with the pressures of anesthetic used. Although the gas hydrates are not formed, the anesthetic will increase the amount of "icebergs" in the water, some of which are present in the absence of the gas. This idea is examined in terms of the "ice cover" at a membrane or the surface of a protein. The amount of this "ice cover" will be proportional to the dissociation pressure of the hydrate, and this may account for the correlation of anesthetic pressures and hydrate dissociation pressures. The increase in "ice cover" on lowering the temperature and its relationship to hypothermia is also examined. Several effects that the "ice cover" might have on nerve conduction and transmission are discussed, and some experi-
ments to test this hypothesis are suggested.

Note added in proof.—Since this article was submitted, a paper by L. Pauling has appeared (Science, 134, 15 (1961)) in which a similar theory is presented. Pauling proposes that microcrystals of hydrate are formed during anesthesia, these crystals being stabilized by side chains of proteins. In spite of any possible stabilization of hydrate crystals by protein side chains, it appears doubtful that crystals could be formed. The gas-filled "icebergs" could be considered equivalent to Pauling's microcrystals, except that the "icebergs" are much smaller and are not crystals in the usual sense.

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1 Miller, S. L., these PROCEEDINGS, (to appear).
2 The term gaseous anesthetic will also be used here for anesthetics which are liquids at room temperature and frequently referred to as volatile anesthetics.
4 The anesthetic pressures from the literature references have been adjusted to the pressure necessary to maintain a person (or animal) in the third plane of the third stage of anesthesia. The pressure of anesthetic necessary to maintain this stage of anesthesia is the figure of interest, since the pressure necessary to induce anesthesia is a problem in rates of transport. Many of the anesthetic pressures given are uncertain, especially for the halogenated hydrocarbons. These values refer mostly to animal experiments which are not strictly comparable to anesthetic action on humans. In many cases there are toxic reactions superimposed on the anesthetic activity which are difficult to allow for.
6 Carpenter, F. G., Am. J. Physiol., 178, 505 (1954). The values given have been normalized by a factor of 1.60.
14 Miller, S. L., unpublished experiments.
17 Stackelberg, M. von, Naturwissenschaften, 36, 327, 359 (1949).
18 Pauling, L., and R. E. Marsh, these PROCEEDINGS, 38, 112 (1952).
The large cavity needed for SF₆ and the (probably) small ΔE may account for its high value of $P_{\text{anesthesia}}/P_{\text{hydrate}}$.