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CURRENT PROBLEMS IN RESEARCH

A Molecular Theory of General Anesthesia

Anesthesia is attributed to the formation in the brain of minute hydrate crystals of the clathrate type.

Linus Pauling

During the last twenty years much progress has been made in the determination of the molecular structure of living organisms and the understanding of biological phenomena in terms of the structure of molecules and their interaction with one another. The progress that has been made in the field of molecular biology during this period has related in the main to somatic and genetic aspects of physiology, rather than to psychic. We may now have reached the time when a successful molecular attack on psychobiology, including the nature of encephalonic mechanisms, consciousness, memory, narcosis, sedation, and similar phenomena, can be initiated. As one of the steps in this attack I have formulated a rather detailed theory of general anesthesia, which is described in the following paragraphs (*1*).

It is likely that consciousness and ephemeral memory (reverberatory memory) involve electric oscillations in the brain, and that permanent memory involves a material pattern in the brain, in part inherited by the organism (instinct) and in part transferred to the material brain from the electric pattern of the ephemeral memory (*2*). The detailed natures of the electric oscillations constituting consciousness and ephemeral memory, of the molecular patterns constituting permanent memory, and of the mechanism of their interaction are not known.

The electric oscillations of the brain make themselves evident in a crude way in electroencephalograms, which show patterns of electric oscillation that depend upon the state of consciousness and the nature of the encephalonic activity of the subject. Evidence that the ephemeral memory, with an effective life that is rarely longer than a few minutes, is electrical in nature is provided by a number of observations. It has been noted that unconsciousness produced by a blow to the head or electric shock often has caused complete loss of memory of the events experienced during the period of 10 or 15 minutes before the blow or shock to the brain. Moreover, when the formation of new permanent memories is interfered with by the decreased ability of the brain to carry on metabolic processes involving proteins, as in old age or Korsakoff's syndrome (alcoholism, protein starvation, thiamine deficiency), the memory continues for a period of 10 or 15 minutes, but usually not much longer; the memory seems to persist only so long as conscious attention is directed to it (*3*).

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Consciousness and Ephemeral Memory

We may discuss the electric oscillations of consciousness and ephemeral memory in terms of the exciting mechanism and the supporting structure. The supporting structure is the brain, with its neuroglial cells, neurones, and synaptic interneuronal connections that determine the detailed nature of the oscillations. The average energy of the electric oscillations may be assumed to be determined by the activity of the exciting mechanism and the impedance of the neural network. Loss of consciousness such as occurs in sleep or in narcosis (general anesthesia) may be the result either of a decrease in activity of the exciting mechanism or of an increase in impedance of the supporting network of conductors, or of both. I think that it is likely that sleep results from a decrease in the activity of the exciting mechanism, and that many sedatives, such as the barbiturates, operate by a specific action on the exciting mechanism, such as to decrease its activity; similarly, stimulants such as caffeine may have a specific action on the exciting mechanism that increases its activity. I think that general anesthetics of the non-hydrogen-bonding type, such as cyclopropane, chloroform, nitrous oxide, and 1,1,1-trifluoro-2-chloro-2-bromoethane (halothane), operate by increasing the impedance of the encephalonic network of conductors, and that this increase in impedance results from the formation in the network, presumably mainly in the synaptic regions, of hydrate microcrystals formed by crystallization of the encephalonic fluid. These hydrate microcrystals trap some of the electrically charged side-chain groups of proteins and some of the ions of the encephalonic fluid, interfering with their freedom of motion and with their contribution to the electric oscillations in such a way as to increase the impedance offered by the network to the electric waves and thus to cause the level of electrical activity of the brain to be restricted to that characteristic of

anesthesia and unconsciousness, despite the continued activity of the exciting mechanism. The formation of the hydrate microcrystals may also decrease the rate of chemical reactions by entrapping the reactant molecules and thus preventing them from coming close enough to one another to react; in particular, the catalytic activity of enzymes may be decreased by the formation of hydrate microcrystals in the neighborhood of their active sites.

Anesthetic Agents

This theory is forced upon us by the facts about anesthesia. Hundreds of substances are known to cause general anesthesia; among them are chloroform ($CHCl_3$), halothane ($CF_3CClBrH$), nitrous oxide (N_2O), carbon dioxide (CO_2), ethylene (C_2H_4), cyclopropane (C_3H_6), sulfur hexafluoride (SF_6) (*4*), nitrogen (N_2) and argon (Ar), which under high pressure cause narcosis (*5*), and xenon (Xe) (*6*). The substances given in this list have rather similar properties as general anesthetics; these properties show a rough correlation with their physical properties, such as the vapor pressure of the liquids. Ferguson (*7*) calls them the physical anesthetics. We may infer that they function in similar ways in causing narcosis. Their chemical properties are such that it is impossible to believe that they produce narcosis by taking part in chemical reactions involving the formation and breaking of ordinary chemical bonds (covalent bonds). Moreover, although it is known that in many physiological processes the formation and rupture of hydrogen bonds play an important part, these substances, with the exception of a few (nitrous oxide, carbon dioxide, chloroform), would not be expected to form even weak hydrogen bonds, and we may call them the non-hydrogen-bonding anesthetic agents. Other narcotics, such as ethanol, may be placed in the hydrogen-bonding class.

The most surprising anesthetic agents are the noble gases, such as xenon. Xenon is completely unreactive chemically. It has no ability whatever to form ordinary chemical compounds, involving covalent or ionic bonds. The only chemical property that it has is that of taking part in the formation of clathrate crystals. In these crystals the xenon atoms occupy chambers in a framework formed by molecules that interact with one another by the formation of hydrogen bonds. The crystal of this sort of greatest interest to us is xenon hydrate, $Xe \cdot 5\frac{3}{4} H_2O$. The crystals of xenon hydrate have been shown by x-ray examination to have the same structure as those of other hydrates of small molecules, such as methane hydrate and chlorine hydrate (*8, 9*). A thorough x-ray examination of chlorine hydrate has been made (*10*), showing that in the cubic unit of structure, with edge 11.88 A, there are 46 water molecules arranged in a framework such that each water molecule is surrounded tetrahedrally by four others, with which it forms hydrogen bonds with length 2.75 A, essentially the same as in ordinary ice (2.76 A). Whereas in ordinary ice the hydrogen-bonded framework does not contain any chambers large enough for occupancy by molecules other than those of helium or hydrogen, the framework for xenon hydrate and related hydrates contains eight chambers per cubic unit cell. Two of these chambers are defined by 20 molecules at the corners of a nearly regular pentagonal dodecahedron, and the other six are defined by 24 water molecules at the corners of a tetrakaidecahedron with 2 hexagonal faces and 12 pentagonal faces. These polyhedral chambers are illustrated in Figs. 1 and 2. The smaller chambers and the larger chambers may be occupied by the xenon atoms or methane molecules, but only the larger chambers permit occupancy by chlorine molecules, which are somewhat larger than the molecules of xenon or methane. In chlorine hydrate the dodecahedral chambers presumably are partially occupied by water molecules not forming hydrogen bonds, or, if air is present, by nitrogen molecules or oxygen molecules.

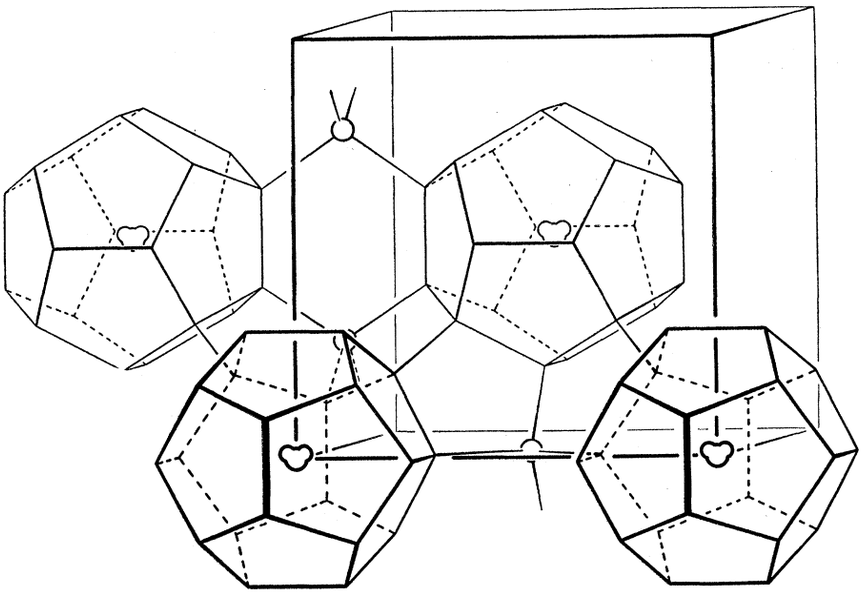

Fig. 1. The structure of the 12-A hydrate crystals of small molecules, such as xenon. The unit cube is about 12 A on an edge. The hydrogen-bonded framework of water molecules consists of 46 water molecules per unit cube. Of these, there are two sets of 20 at the corners of pentagonal dodecahedra, one about the corner of the cube and one about the center of the cube. Six more water molecules aid in holding the dodecahedra together by hydrogen bonds. All hydrogen bonds, indicated by lines in the figure, are about 2.76 A long, as in ordinary ice. There is room in each dodecahedron for a small molecule; a symbol suggesting a molecule of H_2O or H_2S is shown.

Hydrate crystals with somewhat similar structures are formed also by other anesthetic agents (*8, 9*). Chloroform, for example, forms the hydrate $CHCl_3 \cdot 17H_2O$, which has a cubic unit of structure with the cube edge 17.30 A. The hydrogen-bonded framework of 136 molecules per cube involves 16 small chambers per cube, with the pentagonal dodecahedron as the coordination polyhedron, and 8 large chambers, each formed by 28 water molecules at the corners of a hexakaidecahedron, with 4 hexagonal faces and 12 pentagonal faces (Fig. 3). Only the large chambers can accommodate a chloroform molecule. The smaller chambers may be occupied by smaller molecules, such as xenon, which with water and chloroform forms the crystal $CHCl_3 \cdot 2Xe \cdot 17H_2O$. The volume of the 17-A

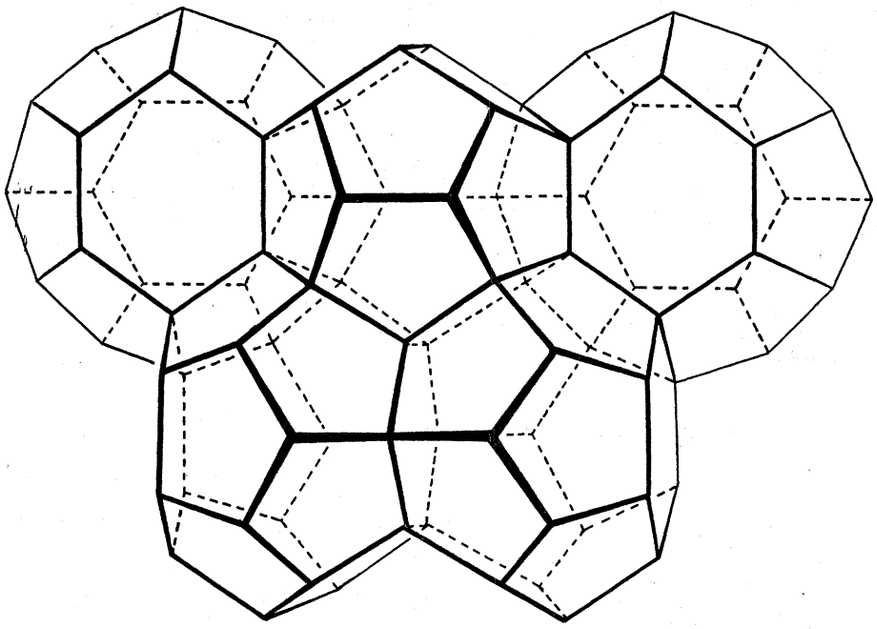

Fig. 2. Another drawing of the structure of the 12-A hydrate crystals. One dodecahedron is shown in the upper center. Around it are tetrakaidecahedra, which provide room for somewhat larger molecules than can fit in the dodecahedra. There are six tetrakaidecahedra and two dodecahedra per unit cube.

framework per water molecule is slightly larger than that of the 12-A framework—an 18-percent increase over ordinary ice (ice I), as compared with 16 percent for the 12-A framework.

The stability of the hydrate crystals results in part from the van der Waals interaction between the entrapped molecules and the water molecules of the framework and in part from the energy of the hydrogen bonds. So far as the energy of the hydrogen bonds is concerned, the stability of the framework alone would be expected to be the same as that of ordinary ice; however, the framework is more open for the hydrates than for ordinary ice, and in consequence the stabilization by van der Waals interaction of the water molecules with one another is less for the hydrate frameworks than for ordinary ice. A thorough study of experimental information about hydrate crystals by the methods of statistical mechanics, with the crystals treated as having variable occupancy of the chambers in the framework, has been carried out by van der Waals and Platteeuv; it shows that the free energy per water molecule of the empty framework is greater than that for ice I at 0°C by 0.167 kcal/mole for the 12-A framework and 0.19 kcal/mole for the 17-A framework (*11*).

The extent to which the crystals are stabilized by the van der Waals interaction of the entrapped molecules and the surrounding water molecules can be estimated by a simple calculation. The London equation for the energy of the electronic dispersion interaction between two molecules A and B is

$$W = -\frac{3}{2}\,\frac{\alpha_A\ \alpha_B\ E_A^*\ E_B^*}{r^6\,(E_A^* + E_B^*)} \qquad (1)$$

In this equation α_A and α_B are the electric polarizabilities of the two molecules, E_A^* and E_B^* are their effective energies of electronic excitation, and r is the distance between their centers.

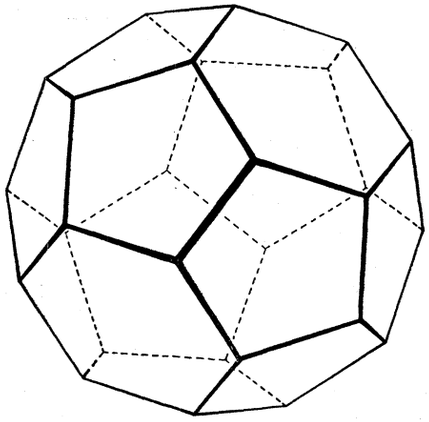

Fig. 3. The hexakaidecahedron formed by 28 water molecules in the 17-A hydrate crystals. The unit cube of these hydrate crystals, such as chloroform xenon hydrate, $CHCl_3 \cdot 2Xe \cdot 17H_2O$, contains 136 water molecules, which define 8 hexakaidecahedra and 16 dodecahedra.

It has been found that agreement between this equation and the observed enthalpies of sublimation of crystals of the noble gases is obtained by taking the effective excitation energy to be 1.57 times the first ionization energy (*12*). The first ionization energy of xenon is 280 kcal/mole, and the same value may be used for the water molecule. The interaction energy of two molecules then has the value $-aR_AR_B/r^6$, in which R_A and R_B are the mole refractions of A and B, in milliliters, and a is equal to 51 kcal/mole, with r measured in angstroms (the mole refraction is $4\pi N/3$ times the polarizability; N is Avogadro's number). In the crystal $8Xe \cdot 46H_2O$, two of the xenon molecules are in pentagonal dodecahedral chambers formed by 20 water molecules at the distance 3.85 A from the xenon atom, and the other six are in tetrakaidecahedral chambers formed by 24 water molecules, of which 12 are at 4.03 A and 12 at 4.46 A. The average energy of van der Waals attraction of a xenon atom ($R = 10.16$ ml) with its neighboring water molecules ($R = 3.75$ ml) is thus calculated to be −9.1 kcal/mole, which becomes −10.3 kcal/mole on addition of the similarly calculated values for the interaction with more distant water molecules and with other xenon atoms in the crystals.

The difference in enthalpy of the 12-A water framework and ordinary ice may be roughly evaluated by a similar calculation of the energy of van der Waals attraction between the water molecules (the nearest and next-nearest neighbors are at nearly the same distances in ordinary ice and the hydrate crystals, but the larger distances are different, corresponding to the more open structure of the hydrate framework). This calculation gives 0.16 kcal/mole for the 12-A framework and 0.20 kcal/mole for the 17-A framework; the close approximation of these values to the corresponding free-energy values indicates that there is little difference in entropy of the empty frameworks and ice I, as is expected from the similarity of the intermolecular forces that determine the vibrations of these hydrogen-bonded structures. The enthalpy of formation, at 0°C, of $Xe \cdot 5\frac{3}{4}H_2O$ from gaseous xenon and ice I is found by experiment (*8*) to be 8.4 kcal/mole. The value given by the foregoing calculations is $10.3 - 5.75 \times 0.16 = 9.4$ kcal/mole, minus a small correction for

the van der Waals repulsion of the xenon atoms and the surrounding water molecules. The agreement shows the extent to which the stabilization of the hydrate crystals may be understood in terms of the van der Waals interactions of the molecules.

The relation between the logarithm of the equilibrium pressure (in millimeters of mercury) of hydrate crystals and water (and also ice I) at 0°C and the mole refraction of the molecules stabilizing the hydrate crystals is shown in Fig. 4, at the left. The energy of van der Waals attraction between the water framework and the entrapped molecules is directly proportional to the mole refraction of the entrapped molecules. Hence if no other interactions affected the free energy of the hydrate crystals the points for $X \cdot 5\frac{3}{4}H_2O$ would lie on a straight line and those for $X \cdot 17H_2O$ on another straight line. There is a general concordance with this expectation, and the deviations are reasonable. For example, the molecules acetylene, ethylene, and ethane increase in size in this order, and it is likely that the van der Waals repulsion between these molecules and the water molecules of their dodecahedral and tetrakaidecahedral cages increases rapidly in this sequence in such a way as to decrease the stability of the ethylene hydrate crystal and, still more, that of the ethane hydrate crystal, with corresponding increases in the equilibrium partial pressures.

Hydrate Microcrystal Theory

It is evident that the mechanism of narcosis cannot be simply the formation in the brain of the hydrate microcrystals $X \cdot 5\frac{3}{4}H_2O$ and $X \cdot 17H_2O$ that we have been discussing, because these crystals would not be stable under the conditions that lead to narcosis. For example, methyl chloride is narcotic for mammals at partial pressure about 0.14 atmosphere and temperature 37°C, but the crystals of its hydrate are not stable at 37° until the partial pressure reaches 40 atmospheres. In order to account for the formation of microcrystals of hydrates at body temperature we must assume that some stabilizing agent other than the anesthetic agent is also operating. I think that it is likely that the other stabilizing agents are side chains of protein molecules and solutes in the encephalonic fluid. It is known that substances resembling the charged side chains of proteins also interact with water to form hydrate crystals with a structure closely resembling that of the hydrates of the anesthetic agents. For example, tetra-*n*-butyl ammonium fluoride forms a hydrate with composition $(C_4H_9)_4NF \cdot 32H_2O$ and melting point 24.9°C. The crystals of this hydrate are tetragonal, with edge $a = 23.78$ A and edge $c = 12.53$ A, and with a structure that is believed to be closely similar in character to that of xenon hydrate and the related hydrates discussed above.

These crystals and similar crystals

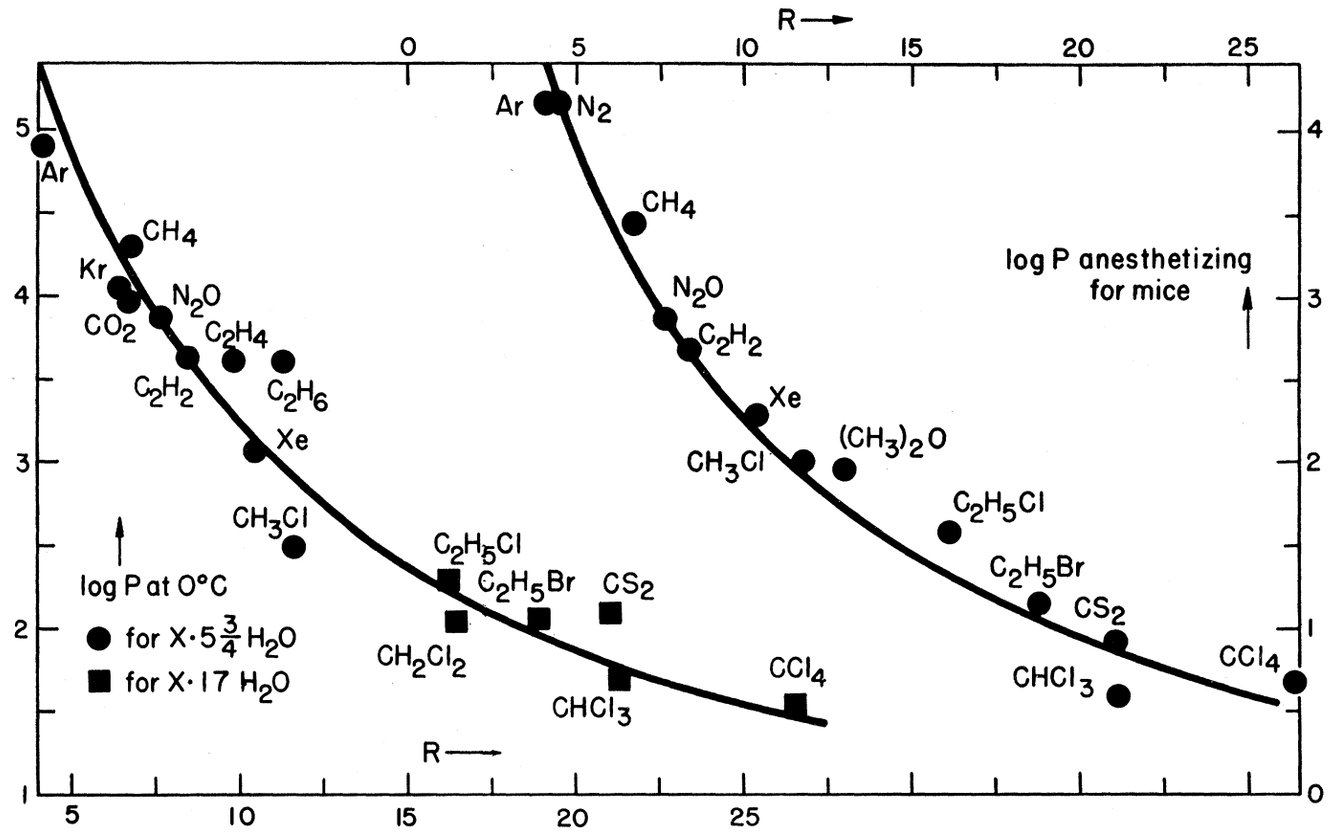

Fig. 4. At left are values of the partial pressure of anesthetic agents in equilibrium with their hydrate crystals and ordinary ice and water at 0°C, plotted against values of the mole refraction (shown by the scale at bottom). Circles correspond to the 12-A hydrate crystals; squares, to the 17-A hydrate crystals. The composition of the 12-A hydrate crystals is $X \cdot 5\frac{3}{4}H_2O$ for the smaller molecules, which can occupy both dodecahedra and tetrakaidecahedra, and $X \cdot 7\frac{2}{3}H_2O$ for the larger ones (ethane, methyl chloride), which occupy only the tetrakaidecahedra. At right the logarithm of the anesthetizing partial pressure for mice is plotted against the mole refraction of the anesthetizing agent (scale at top).

of tetra-*i*-amyl ammonium salts were first made by Fowler, Loebenstein, Pall, and Kraus (*13*). The determinations of the structure of these crystals and of related ones that they have prepared $\{[(n\text{-}C_4H_9)_3S]F \cdot 20H_2O$, $[(i\text{-}C_5H_{11})_4N]F \cdot 38H_2O$, $[(n\text{-}C_4H_9)_4P]_2WO_4 \cdot 64H_2O\}$ are being carried out by Jeffrey and his co-workers (*14*).

It is known that two anesthetic agents can cooperate to increase the stability of a hydrate framework. For example, 1 atmosphere of xenon (*15*) increases the decomposition temperature of the 17-A hydrate of chloroform by a little over 14.7°C. In the absence of xenon the crystal has the composition $CHCl_3 \cdot 17H_2O$, and in its presence $CHCl_3 \cdot 2Xe \cdot 17H_2O$. The 17-A framework forms one hexakaidecahedron and two dodecahedra per $17H_2O$; the chloroform molecules are too large to enter the dodecahedra, which can, however, be occupied by atoms of xenon or other small molecules. Similar increases of 5° to 20°C in the decomposition temperatures of 17-A hydrate crystals of $CHCl_3$, CH_3CF_2Cl, $CHF{=}CF_2$, $CFCl_3$, SF_6, and some other substances by 1 atmosphere of krypton, H_2S, or H_2Se, as well as by xenon, have also been reported (*8*, *15*). The 17-A hydrate $CHF_2CH_3 \cdot 2H_2S \cdot 17H_2O$ becomes stable in the presence of H_2S, whereas 1,1-difluorethane without other molecules forms a 12-A hydrate.

We may accordingly surmise that the stabilizing effect for hydrate crystals of amino acids and other solute molecules in encephalonic fluid and also of the alkyl ammonium side chains of lysyl residues and the alkyl carboxylate ion side chains of aspartate and glutamate residues, and perhaps also of certain other side chains of proteins, could operate effectively to stabilize hydrate crystals at temperatures not much lower than normal body temperature, perhaps about 25°C. The narcosis resulting from cooling of the brain, which is observed to take place at about 27°C in human beings, would then, according to our theory, be explained as resulting from the formation of these hydrate crystals in the synaptic regions of the brain and from the resultant increase in impedance of the neural network and correspondingly decreased energy of the electric oscillations. Hibernation may similarly involve the induction of unconsciousness by formation of hydrate crystals on decrease in temperature.

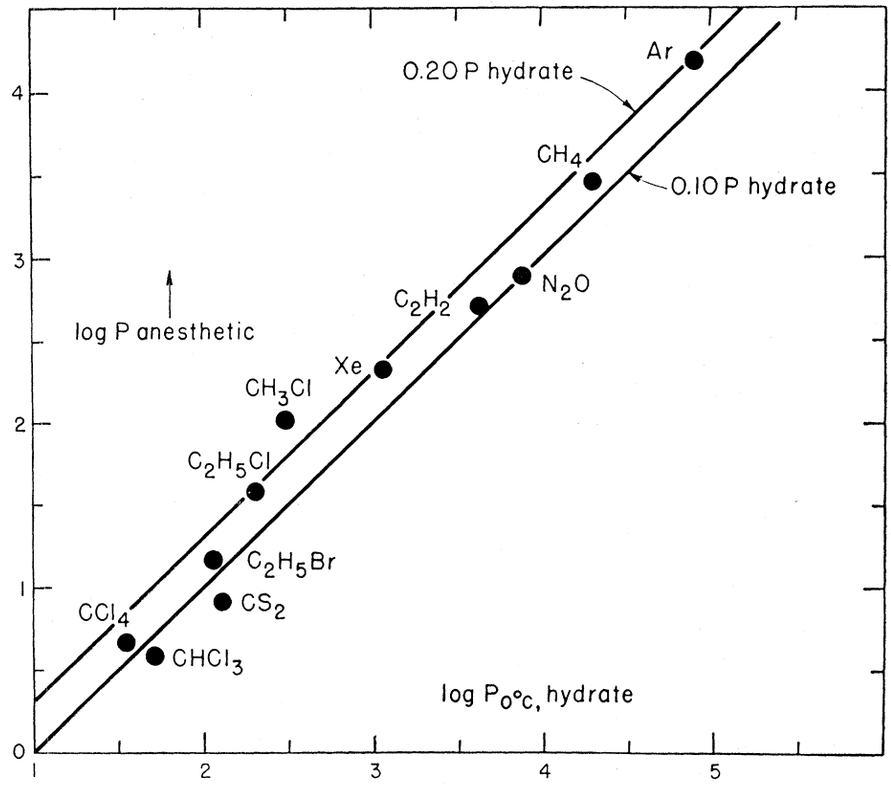

Fig. 5. A diagram showing the logarithm of the anesthetizing partial pressure of non-hydrogen-bonding anesthetic agents plotted against the equilibrium partial pressure of their hydrate crystals.

The molecules of the anesthetic agent, when present, would occupy some of the chambers in the hydrate crystal, with others occupied by the protein side chains and other groups normally present in the brain, in such a way as to give an increase in stability of the microcrystals such as to permit them to form at a temperature 10° or 15°C higher than that at which they are stable in the absence of the anesthetic agent. Through the formation of these microcrystals the conductance of the network would be decreased, with a consequent decrease in energy of the electric oscillations sufficient to cause unconsciousness. On decrease of the activity of the anesthetic agent in the encephalonic fluids, as elimination from the body takes place, the microcrystals would melt, the conductance of the synapses would be restored to its original level, and consciousness would be regained.

The logarithm of the anesthetizing partial pressure (in millimeters of mercury) for mice is shown as a function of the mole refraction of the non-hydrogen-bonding anesthetic agents in Fig. 4, at the right. The points lie close to a curve that resembles the curve for the equilibrium partial pressure of the hydrate crystals, shown at the left. The relation between the anesthetizing partial pressure and the partial pressure for the hydrate crystals at 0°C is shown in Fig. 5; the two pressures are proportional, the proportionality factor being about 0.14. The average deviation of the 11 points from the best line corresponds to the factor 1.4 (or 0.7) over a total pressure range of 4000 (for the logarithm, $\pm$ 0.15 over a range of 3.6).

Other Theories of Anesthesia

This agreement provides some support for the proposed theory, but not proof. Approximately the same correlation would be found between the anesthetizing partial pressure of the non-hydrogen-bonding anesthetic agents and any other property involving an energy of intermolecular interaction proportional to the mole refraction of the molecules. An example is the solubility in olive oil of the gaseous anesthetic agent at a standard pressure; another is the ratio of the solubility in olive oil to that in water (the oil-

water distribution coefficient). The first depends largely on the energy of van der Waals attraction of the anesthetic molecules by the oil molecules, and the second on the difference between this energy and the energy of attraction by the water molecules, and each is proportional to the mole refraction of the anesthetic agent. These quantities are involved in the Meyer-Overton theory of narcosis (*16*). The thermodynamic activity theory of Ferguson (*7*) is based upon the observed rough constancy of the ratio of anesthetizing partial pressure of non-hydrogen-bonding anesthetic agents to the vapor pressure (thermodynamic activity) of the pure liquid at a standard temperature. This rough constancy is, of course, to be expected on any theory of anesthesia involving intermolecular forces, since the vapor pressure of a liquid is determined by the forces acting between its molecules.

The lipid theories of anesthesia seem to me to be less attractive than the hydrate microcrystal theory. First, brain, like other tissues of the human body, consists largely of water: about 78 percent, as compared with about 12 percent of lipids and 8 percent of proteins. The water contains ions and proteins with electrically charged side chains and is hence expected to be largely involved in the electric oscillations that constitute consciousness; the lipids probably function mainly as insulating materials, and their electrical properties are presumably changed only slightly by the presence of nonpolar solute molecules of the non-hydrogen-bonding anesthetic agents. Moreover, the postulated change in phase from liquid to hydrate microcrystal, with a correspondingly great change in properties, provides an explanation of the large change in encephalonic activity caused by a small amount of substance, and there is no evidence to cause us to expect such a change in phase for the lipids.

Agents That Function by Stabilization of Microcrystals

Anesthetic agents that function by the stabilization of hydrate microcrystals may be divided into several classes, determined by the sizes and shapes of their molecules. Those of the first class may be defined as having molecules sufficiently small to fit into a pentagonal dodecahedron formed by 20 hydrogen-bonded water molecules without serious van der Waals repulsion. Those of the second class include the larger molecules that are able to fit into the hexagonal tetrakaidecahedron without serious van der Waals hindrance. Those of the third class are the still larger molecules that fit into the hexakaidecahedron without serious steric hindrance. The molecules of other classes might fit into larger chambers in the hydrogen-bonded framework; for example, the tetra-*n*-butyl ammonium ion probably fits into the cavity formed by four contiguous tetrakaidecahedra about the tetrahedral position between four dodecahedra in the chlorine hydrate structure, with the elimination of the water molecule at this position, as found in the crystal-structure study of the trialkylsulfonium crystal carried out by Jeffrey and McMullan (*14*). It seems likely that several kinds of microcrystals are formed in brain tissue, and that they are variously stabilized by anesthetic agents of the several classes. It might accordingly be expected that the agents of different classes would act to some extent synergistically (and also to some extent competitively, in that molecules of an agent of one class can occupy the larger polyhedra corresponding to the succeeding classes, with, however, less stabilizing effect than for its own polyhedron because of the greater intermolecular distance). Hence it may be suggested that a mixture of agents of the dodecahedral, tetrakaidecahedral, and hexakaidecahedral classes, such as CF_4, CF_3Cl (or CF_2Br), and $CFCl_3$ (or $CF_3CClBrH$), would be a better anesthetic than any one substance.

It is not unlikely that magnesium ion, $Mg(OH_2)_6^{++}$, acts as an anesthetic agent by stabilizing hydrate microcrystals. This ion, with its attached water molecules, would become a part of the hydrogen-bonded framework. Molecules such as ethanol and tribromoethanol, CBr_3CH_2OH, may be expected to participate in the formation of microcrystals of hydrates in such a way that the molecule becomes a part of the hydrogen-bonded framework and also has a space-filling and van der Waals stabilizing effect. Other hydrogen-bond-forming narcotic agents may attach themselves by the formation of hydrogen bonds to protein molecules in a specific way so as to interfere specifically with certain encephalonic processes. The study of these specific effects will require the detailed investigation of the proteins and other substances present in brain and nerve tissue.

Related Studies

Many experiments by means of which evidence about the proposed molecular theory of anesthesia may be obtained are suggested by the theory; some of them are being carried out in our laboratories. Studies of crystalline hydrate phases formed in the presence of anesthetic agents, ions, and protein molecules or molecules and ions similar to protein side chains might yield interesting results.

The "iceberg" theory of ionic solutions (*17*) and of hydration of proteins (*18*) is closely related to the hydrate microcrystal theory of anesthesia; the only change suggested for these theories is that the ordered arrangement of water molecules about the solute ions and protein side chains has one or another of the clathrate structures rather than the more compact ice-I structure.

The hydrate microcrystal theory of anesthesia clearly suggests that the anesthetic agents should act on all tissues, and not just on brain and nerve tissue. It was pointed out nearly a century ago by Claude Bernard (*19*) that "an anesthetic agent is not just a special poison of the nervous system; it anesthesizes all elements, all tissues by numbing them, temporarily blocking their irritability." Many studies of the effects of anesthetic agents on physiological processes other than thinking have been reported (*20*).

At present there is little information available about the fraction of the aqueous phase in the brain that is changed into hydrate microcrystals during anesthesia, or about the dimensions of the microcrystals. Experiments now under way should provide some information. The results of density-gradient ultracentrifuge studies of solutions of deoxyribonucleic acid by Hearst and Vinograd (*21*) indicate that at 25°C the nucleic acid molecules have about 50 water molecules of hydration per nucleotide residue at water activity near unity. This suggests that the microcrystals have linear dimensions of about 20 A or 30 A (for nucleic acid, of course, they continue along the Watson-Crick double helix). A hydrate cube with edge 30A contains about 750 water molecules.

Conclusion

The hydrate-microcrystal theory of anesthesia by non-hydrogen-bonding agents differs from most earlier theories in that it involves primarily the interaction of the molecules of the anesthetic agent with water molecules in the brain, rather than with molecules of lipids. The postulated formation of hydrate microcrystals similar in structure to known hydrate crystals of chloroform, xenon, and other anesthetic agents as well as of the substances related to protein side chains, entrapping ions and electrically charged side chains of protein molecules in such a way as to decrease the energy of electric oscillations in the brain, provides a rational explanation of the effect of the anesthetic agents in causing loss of consciousness. The striking correlation between the narcotizing partial pressure of the anesthetic agents and the partial pressure necessary to cause formation of hydrate crystals provides some support for the proposed theory, but it is recognized that any theory based upon the van der Waals attraction of the molecules of the anesthetic agent for other molecules would show a similar correlation, inasmuch as the energy of intermolecular attraction is approximately proportional to the polarizability (mole refraction) of the molecules of the anesthetic agent. The proposed theory is sufficiently detailed to permit many predictions to be made about the effect of anesthetic agents in changing the properties of brain tissue and other substances, and it should be possible to carry out experiments that will disprove the theory or provide substantiation for it.

References and Notes

1. The work reported in this article (contribution No. 2697) is part of a program of investigation of the chemical basis of mental disease supported by grants to the California Institute of Technology made by the Ford Foundation and the National Institutes of Health. This theory has been presented in lectures at Pacific State Hospital, California State Department of Mental Hygiene, Spadra (23 May 1960); at a meeting of the Western Society of University Anesthetists, Stanford Medical School, Palo Alto, Calif. (21 Jan. 1961); at a meeting of the Hawaii section of the American Chemical Society and Sigma Pi Sigma, University of Hawaii, Honolulu (5 Apr. 1961); and at a meeting of the Mediterranean section of the Société de Chimie Physique, Toulouse, France (25 Apr. 1961).
2. L. A. Jeffress, Ed., *Cerebral Mechanisms in Behavior* (Wiley, New York, 1951), especially sections by W. S. McCulloch. McCulloch (p. 101) suggests that there are three kinds of memory: (i) reverberatory memory; (ii) a kind of alteration of the nervous net with use; and (iii) a storage memory with a bottleneck both in putting information in and in taking it out. If the second and third are to be differentiated at all, I think that they may be classed together as involving permanent or semipermanent molecular patterns.
3. McCulloch (*2*, p. 58) has reported an example of a man over 80 years old, and with no power of adding to his permanent memory, who held all the details of an important meeting of a board of directors in his mind during the 8 hours of its duration, so that he was able to summarize it brilliantly during the last half hour of the meeting; yet a few minutes after the meeting he had forgotten it completely and permanently.
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