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The Membrane Actions of Anesthetics and Tranquilizers

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. . . let us remember that chloroform does not act solely on the nerve tissues. Far from that, it has an action on all the tissues and attacks each one at a time which is a function of its susceptibility. . . . An anesthetic is not a special poison for the nervous system. It anesthetizes all the cells, benumbing all the tissues, and stopping temporarily their irritability. . . . We can study elsewhere than in the central nerve cells the phenomenon which causes this stoppage of action and. . . . It is permissible to assume that something similar happens in the nerve cell.

Claude Bernard
Leçons sur les anesthésiques et sur l'asphyxie, 1875 (37 a, 363)

THESE words of Bernard clearly anticipated the fact that many, if not most, of the membrane actions of anesthetics and tranquilizers occur in both excitable and non-excitable membranes. These similar actions justify the use of simple membranes to determine the concentrations of anesthetic in the excitable membrane and to resolve the molecular pharmacology of anesthesia. The purpose of this review is to summarize the data available on the membrane concentrations of anesthetics, and to try to relate these data to the membrane actions of anesthetics and tranquilizers.

It continues to be generally assumed that the primary actions of anesthetics are on the cell membrane (plasmalemma) rather than on intracellular processes (66). This assumption is warranted by three types of observations:

1) Perfused axons, from which all the axoplasm has been removed, are still readily blocked by anesthetics (209, 210, 432, 433, 435).

2) Action potentials in artificial lipid bilayers are blocked by anesthetics such as cocaine or chlorpromazine (421).

3) Nerve block and synaptic block occur at concentrations of anesthetic which are lower than those required to inhibit metabolism and oxygen consumption (355–358).

Other studies, however, provide evidence that the primary anesthetic action is on intracellular organelles such as mitochondria (226, 489) or microtubules (14, 15, 445; but see 201a). These intracellular actions, on the other hand, occur at anesthetic concentrations which are usually 5 to 20 times higher than those required to block the action potential (355–358).

The most general definition of an anesthetic is a drug which, when applied directly to the nerve or muscle cell, reversibly blocks the action potential without appreciably affecting the resting membrane potential (within 4–5 mV) of the cell (47, 64, 561, 611). According to this definition, a wide variety of lipid-soluble compounds are anesthetic, including tranquilizers, anticonvulsants, antihistamines, steroids, detergents, anti-arrythmics, narcotics, vasodilators and sedatives, as listed in table 1.

In addition to these reversible anesthetics listed, there are irreversible anesthetics, such as the haloalkylamines (505, 508), which give sustained anesthetic action on nerves. These compounds alkylate the excitable membrane and remain attached to the membrane, presumably without depolarizing or killing the nerve cell.

TABLE 1
Families of anesthetics

I. Electrical Stabilization of the Membrane by Anesthetics and Tranquilizers

Before reviewing the non-electrical effects of anesthetics on membranes and analyzing the data on the membrane concentrations of anesthetics (section II), it is appropriate to summarize the electrical effects of anesthetics on cell membranes.

The work of Hodgkin *et al.* has established that the rising phase of the action potential is associated with a rapid entry of sodium ions into the cell (269, 503; see 562 for a review), although recently it has been found that about 1% of this sodium-current may be attributed to the entry of calcium ions (34).

Weidmann in 1955 (652a) and Thesleff in 1956 (611) observed that the rate of rise of the action potential was reduced by a variety of anesthetics. [Separate studies by Straub in 1956 (595) had shown that procaine slightly reduced the changes in resting membrane potential produced by altering the external Na^+ concentration; the effect of an anesthetic on resting permeability, however, does not indicate what the effect may be on the ionic permeability during the impulse (549).]

Thesleff's findings (611) have also been observed for a variety of anesthetics, including procaine (23, 293, 608), lidocaine (265), prochlorperazine (265), barbiturates (64, 432), alcohols (25, 278, 295, 418), detergents (328), ether (294),

TABLE 1

Families of anesthetics

		moles/liter				moles/liter				moles/liter		
1. Standard local anesthetics (hydrochlorides)				***3. Volatile anesthetics (see tables 2–5)***				***10. Steroids***			
Procaine	Frog sciatic n.	1.25×10^{-3}	(376)	Ether	Frog sartorius m.	$\sim 3.8 \times 10^{-4}$	(294)	Hydroxydione	Rat phrenic n.	1.3×10^{-5}	(393)
	Frog sciatic n.	1×10^{-3}	(47)	***4. Inert and gaseous anesthetics (see tables 2–5)***				***11. Antihistamines***			
	Frog sciatic n.	1×10^{-3}	(595)								
	Frog sciatic n.	4.6×10^{-3}	(573)								
	Frog sciatic n.	2.5×10^{-3}	(595)	***5. Intravenous anesthetics***				Pyribenzamine	Frog sciatic n.	$\sim 1.7 \times 10^{-5}$	(134a)
	Lobster axon	8×10^{-3}	(530)					Diphenhydramine	Frog sciatic n.	$\sim 2\text{-}3 \times 10^{-5}$	(134a)
	Squid axon	5×10^{-3}	(507)	Urethane	Frog Ranvier node	1.68×10^{-1}	(631)		Calf Purkinje f.	$\sim 4 \times 10^{-5}$	(652a)
	Squid axon	$>3.7 \times 10^{-3}$	(608)	Chloralose	Frog sartorius m.	$>8 \times 10^{-3}$	(611)	Chlorpheniramine	Squid giant axon	5×10^{-4}	(507)
	Frog sartorius m.	2×10^{-3}	(293) (130, 378)								
Cocaine	Frog sciatic n.	5×10^{-3}	(376)	***6. Anticonvulsants***				***12. Anti-Parkinsonian drugs***			
	Frog sciatic n.	4×10^{-3}	(47)								
	Frog sciatic n.	2.6×10^{-3}	(573)	Paraldehyde	Frog sartorius m.	$\gg 6 \times 10^{-3}$	(611)	Trihexyphenidyl	Squid giant axon	3×10^{-4}	(507)
	Frog sciatic n.	$\sim 1.5 \times 10^{-3}$	(61)	Trimethadione	Squid giant axon	$\sim 5 \times 10^{-3}$	(507)	Caramiphen	Squid giant axon	2×10^{-4}	(507)
	Calf Purkinje f.	$\sim 5 \times 10^{-3}$	(652a)	Diphenylhydantoin	Squid giant axon	$>1 \times 10^{-3}$	(507)		Frog sciatic n.	1×10^{-4}	(621)
Lidocaine	Frog sciatic n.	3.8×10^{-3}	(376)		Crayfish receptor	$\sim 1 \times 10^{-4}$	(31)				
	Frog Ranvier node	1×10^{-3}	(265)					***13. Anti-arrhythmics***			
Tetracaine	Squid giant axon	1×10^{-4}	(507)	***7. Narcotics***							
Dibucaine	Frog sciatic n.	1×10^{-3}	(47)					Propanolol	Mouse tail n.	3.9×10^{-3}	(261)
				Morphine	Squid giant axon	1×10^{-3}	(200)		Adrenergic n.	$>8 \times 10^{-5}$	(41)
2. Alcohols					Squid giant axon	1×10^{-3}	(572)	Procaine amide	Calf Purkinje f.	$\sim 1.8 \times 10^{-4}$	(652a)
				Levorphanol	Squid giant axon	1×10^{-3}	(572)	Quinidine sulphate	Calf Purkinje f.	$\sim 1.3 \times 10^{-5}$	(652a)
Methanol	Lobster axon	4.45	(278)	Dextrorphan	Squid giant axon	1×10^{-3}	(572)				
	Frog sciatic n.	1.6	(427)	Levallorphan	Squid giant axon	1×10^{-5}	(572)	***14. Muscle relaxants***			
Ethanol	Lobster axon	1.8	(278)								
	Squid axon	~ 1.5	(25)	***8. Hypnotics and sedatives***				Benzimidazole	Frog sciatic n.	6.5×10^{-3}	(621)
	Squid n.	>1.1	(418)					Mephenesin	Frog sciatic n.	5×10^{-3}	(621)
	Frog sartorius m.	$>6 \times 10^{-1}$	(295)	Barbital	Squid giant axon	2×10^{-1}	(507)				
	Frog sciatic n.	5.5×10^{-1}	(427)	Pentobarbital	Squid giant axon	$>6 \times 10^{-3}$	(64)	***15. Anti-inflammatory drugs***			
Propanol	Lobster axon	5.5×10^{-1}	(278)		Frog sciatic n.	$\sim 5 \times 10^{-3}$	(337)				
	Squid axon	$\sim 3.8 \times 10^{-1}$	(25)		Frog sartorius m.	$\sim 2 \times 10^{-3}$	(611)	Salicylic acid	Rabbit vagus C	3×10^{-3}	(534a)
	Frog sciatic n.	2.18×10^{-1}	(579)	Amobarbital	Frog sciatic n.	4×10^{-3}	(531)	Flufenamic acid	Rabbit vagus C	1×10^{-3}	(534a)
	Frog sciatic n.	1.6×10^{-1}	(427)	Phenobarbital	Squid giant axon	1×10^{-1}	(507)	Niflumic acid	Rabbit vagus C	1×10^{-3}	(534a)
Butanol	Lobster axon	1.1×10^{-1}	(278)		Frog sciatic n.	$\sim 5 \times 10^{-3}$	(337)	Mefenamic acid	Rabbit vagus C	5×10^{-4}	(534a)
	Frog sciatic n.	6.8×10^{-2}	(579)	Chloral hydrate	Frog sartorius m.	$\gg 9 \times 10^{-3}$	(611)	Phenylbutazone	Rabbit vagus C	5×10^{-4}	(534a)
Pentanol	Frog sciatic n.	4.5×10^{-2}	(61)	***9. Tranquilizers***				Oxyphenbutazone	Rabbit vagus C	2.5×10^{-4}	(534a)
	Squid axon	$\sim 2.5 \times 10^{-2}$	(25)					***16. Detergents***			
	Frog sciatic n.	2.1×10^{-2}	(579)								
	Lobster axon	2.1×10^{-2}	(278)	Chlorpromazine	Squid giant axon	$\sim 8 \times 10^{-5}$	(507)				
Octanol	Squid axon	$\sim 4.5 \times 10^{-4}$	(25)	Ethopropazine	Squid giant axon	$\sim 8 \times 10^{-5}$	(507)	Sodium lauryl sulphate	Squid axon	$\sim 1 \times 10^{-4}$	(328)
Benzyl alcohol	Lobster axon	3.5×10^{-2}	(530)	Prochlorperazine	Frog node	5×10^{-5}	(265)				

morphine (209) and miscellaneous local anesthetic derivatives (210, 433, 435). Virtually all of these drugs just cited reduced the sodium conductance at concentrations below those affecting the resting membrane potential. In most instances, the action potential was abolished without appreciable effect on the resting membrane potential.

Earlier studies reporting marked depolarization (61, 427) or hyperpolarization (53, 480, 481) by organic solvents, ether and aliphatic alcohols, employed membrane-lytic concentrations of anesthetics (see section III) or did not state the concentrations at which the effect occurred (53, 480, 481). There does not seem to be any different action on the squid or lobster axon membrane potential between short and long-chain alcohols (25, 278). Knutsson (330) and Knutsson and Katz (331) did find that low concentrations of ethanol (0.05–0.1 M) usually depolarized frog skeletal muscle by approximately 5 mV in 30 min, but he also found instances where no change of the membrane potential was perceptible. Inoue and Frank (295) report that ethanol up to 0.57 M only depolarized the frog skeletal muscle cell membrane by 4 to 5 mV but that this depolarization was insufficient by itself to cause inexcitability; they noted, furthermore, that there was no difference in the membrane resting potentials between blocked muscle fibers and unblocked muscle fibers within the same muscle. Since some anesthetics can also hyperpolarize cell membranes [*e.g.*, cyclopropane hyperpolarizes gastrocnemius by 4 mV; (326a)], there does not seem to be any clear relation between membrane potential and block of membrane excitability.

Shanes (561, 574) used the word "stabilizers" for the anesthetics because they blocked membrane excitability without appreciably altering the resting membrane potential. Since it is now known that these lipid-soluble anesthetics can "fluidize" and disorder the membrane (396–398, 469, 555), it is more appropriate to use the term "electrical stabilizers" for the anesthetic drugs.

Not only do the anesthetics electrically stabilize the membrane from depolarization, but there are indications that they may also block various forms of hyperpolarization; for example, 10^{-4} M diphenylhydantoin decreases the membrane excitability of the crayfish stretch receptor as well as abolishes the post-tetanic hyperpolarization (31); halothane completely blocks the 7 mV hyperpolarization (gastrocnemius) induced by epinephrine infusion (326a). There is insufficient work, however, on the effects of anesthetics on hyperpolarization responses of the nerve cell.

The block of membrane excitability caused by anesthetics can be partially antagonized by raising the concentration of Na^+ in the extracellular fluid (130, 293–295, 378, 631–633).

The anesthetic concentration to depress the K^+-conductance of the action potential is generally about 10 times higher than that required to depress the Na^+-conductance channel (25, 264, 265, 328; see refs. 264, 266–268 for discussion of ion channels).

Finally, it should be mentioned that the anesthetic concentration just necessary for conduction block is smaller than that necessary to inhibit local excitation (631, 633). This means that although anesthetized cells may not conduct impulses, they will respond locally and electrotonically if stimulated strongly.

For any particular hypothesis to be termed a "theory of anesthesia," it is necessary for that hypothesis to explain the manner in which the sodium conductance channel is inhibited or the manner in which synaptic transmission is modified. Otherwise, if the hypothesis merely shows a correlation of anesthetic potency with some physicochemical parameter, the hypothesis is essentially only a rule of anesthesia.

II. The Membrane Concentrations of Anesthetics and Tranquilizers

Having surveyed in section I the types of drugs which directly block excitable cells, the question arises as to whether these chemically different compounds block the sodium conductance channel in the same way or not.

In order to answer this question, it is essential to know the concentrations of these drugs in the membrane phase. The classical work of Hans H. Meyer (399–401), Baum (45), Overton (461, 461a) and Kurt H. Meyer (402–404) has established that the potency of an anesthetic is directly proportional to its oil/water partition coefficient. This has led to the Meyer-Overton rule of anesthesia: "Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipoids of the cell" (401, 402). This rule was supported by the kind of data tabulated in references 401 and 402, a sample of which is shown here (from 401):

Anesthetic	Subject	(Olive Oil/Water) Coefficient	Anesthetic Concentration in Air	Anesthetic Concentration in Olive Oil
			vols. %	*moles/l oil*
Nitrogen	Frog	0.05	9000	0.18
Methane	Mouse	0.54	370	0.08
Ethylene	Mouse	1.3	80	0.04
Nitrous oxide	Mouse	1.4	100	0.06
Diethylether	Mouse	50	3.4	0.07
Pentane	Mouse	37	13.2	0.19
Chloroform	Mouse	265	0.5	0.05

The average concentration of anesthetic (in the oil phase) for a variety of anesthetics is between 0.03 and 0.06 moles drug per liter of oil when considering general anesthesia (24, 260).

The major problem in testing the validity of the Meyer-Overton rule is that olive oil does not have the chemical composition of the biological membrane which is composed of about 40 to 50% protein, 5 to 10% carbohydrate and has a lipid composition very different from that of olive oil. There is no agreement on which organic solvent best simulates the hydrophilic-hydrophobic nature of the biological membrane. Some researchers have preferred to study the correlation between anesthetic potency and anesthetic partitioning into a monolayer/water system (124, 125, 575, 579). The partition coefficients of anesthetics have also been determined in many different solvent/water systems, including isobutanol, benzene (127, 128), ether (127, 128, 205), oleic alcohol (127, 376), octanol (215, 253, 254, 365, 366, 392, 429) and amyl acetate (89). It is generally realized, how-

ever, that the interaction energies between the anesthetic and the solvent may differ considerably from those existing within the biological membrane.

Since there was no simple way to measure the molar concentration of anesthetic in the cell membrane, Ferguson in 1939 calculated the thermodynamic activity of the anesthetic in the anesthetized animal (199, 200). Since the anesthetic state is a true and reversible equilibrium (170, 172), the thermodynamic activity is the same in all the phases of the organism, including the cell membrane. Ferguson, as well as Brink and Posternak (80), calculated that equinarcotic effects occurred when the thermodynamic activity was between 0.01 and 0.1 mole fraction for a variety of neutral anesthetics (see also 24, 135).

A major difficulty in using the thermodynamic activity calculations is that they are mostly based on the use of pure liquid anesthetic as the standard state (80). This means that the thermodynamic activity, as usually calculated, reflects the work per molecule required to transfer the anesthetic from the pure liquid phase to the membrane phase. Since the interaction energies between the molecules in each of the pure liquid anesthetics will probably be different, Schneider (532) has pointed out the appropriate standard state is that of the infinitely dilute solution. Experimentally this is a difficult standard to use because it requires precise vapor pressure determinations (80, 96–98).

The most direct way to test the validity of the Meyer-Overton rule of anesthesia is to measure both the anesthetic potency and the anesthetic concentration in the membrane phase on the same biological cell. This is feasible with human erythrocytes.

With the advent of subcellular fractionation technique, it is now possible to isolate membranes and to examine the purity of the fraction by electron microscopy. The adsorption of the following anesthetics and tranquilizers to cell or subcellular membranes has been studied: reserpine to sarcoplasmic reticulum (36); chlorpromazine and other phenothiazine tranquilizers and antihistamines to erythrocyte membranes (8, 346, 542, 556), muscle membranes (36, 511) and synaptosomes (511); inert and gaseous anesthetics to erythrocyte membranes (332, 483); alcohols and phenols to erythrocyte membranes (129, 511, 553); local anesthetics to myelin (575), to squid axon membrane (624), to erythrocyte and synaptosome membranes (512); progesterone and steroids to erythrocyte membranes (2, 160, 449), to liver cell membranes (235), to lysosomes (604) and to artificial phospholipid/cholesterol membranes (582); narcotics (439), xenon (345) and anticonvulsants (443) to brain membranes or particulates (see also 511); and fatty acids to erythrocytes (229).

For the study of molecular events involved in the membrane action of anesthetics, a cell is required which responds to all anesthetics and which has a membrane that can be readily isolated. Erythrocytes may serve this purpose both qualitatively and quantitatively, for the following reasons:

1) All lipid-soluble anesthetics (*e.g.*, those in table 1) protect erythrocytes from hypotonic hemolysis, examples of which are shown in Figures 1A, 2A and 3 for the alcohols, chlorpromazine and miscellaneous drugs, respectively (see also 509). Drugs with extremely low lipid solubility, including tetrodotoxin, do not protect

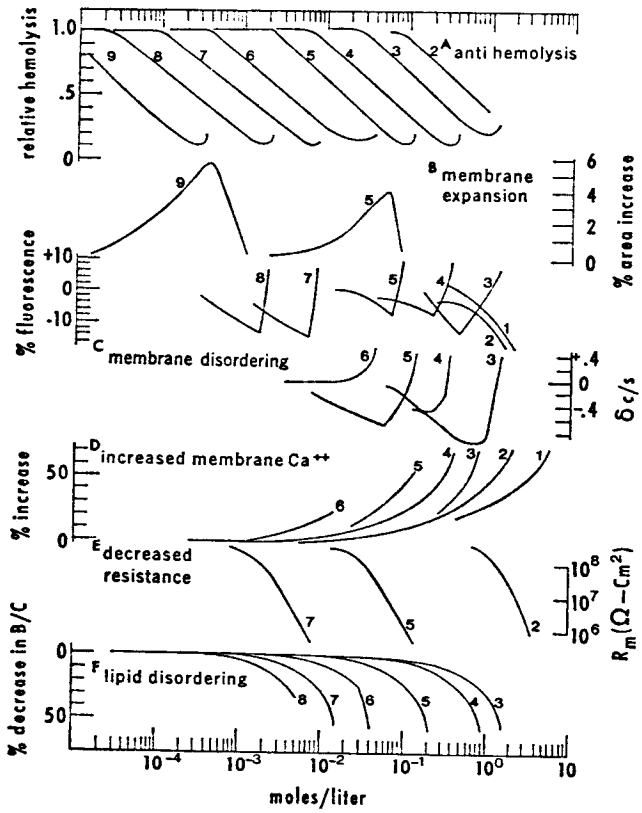

FIG. 1. A summary of the membrane actions of the aliphatic alcohols. Number 1 represents methanol, number 2 is propanol, *etc.*, up to 9 which represents nonanol. A, the antihemolytic or protective effects of alcohols against osmotic hemolysis of human erythrocytes (509–511, 540, 553), where a relative hemolysis of 1.0 indicates about 30% absolute hemolysis. B, the percent of increase in membrane area of spherical erythrocyte ghosts, derived from monitoring the cell volumes by Coulter counter techniques (550), and where the area of a normal erythrocyte is about 135 μ^2. C (upper half), membrane disordering as seen by a fall in the percent of fluorescence of ANS adsorbed to erythrocyte ghost membranes (Spero and Roth, unpublished). C (lower half), membrane disordering as monitored by NMR methods and indicating that the "membrane viscosity" is reduced; δ is the c/s change in relaxation rate of the membrane-probing benzyl alcohol molecules (396, 397). D, showing that the alkanols increase the amount of membrane-bound Ca^{++} in erythrocyte ghost membranes (547). E, fall in resistance of lipid bilayers (adapted from 242). F, disordering of oriented and spin-labeled lipid multilayers, as monitored by electron spin resonance, and where percent decrease in b/c represents the percent of drop in the ratio of the amplitudes of the ESR signal (adapted from 469). Note that high and lytic concentrations of the alcohols cause effects opposite to low concentrations in most instances. The experimental points have been deleted for sake of clarity.

erythrocytes (509). [It has been stated that tetrodotoxin does not block the sodium current of the denervated sarcolemma (256a, 493); substantial evidence indicates, however, that the denervated membrane is merely less sensitive to tetrodotoxin and remains normally sensitive to batrachotoxin (13a, 13b).]

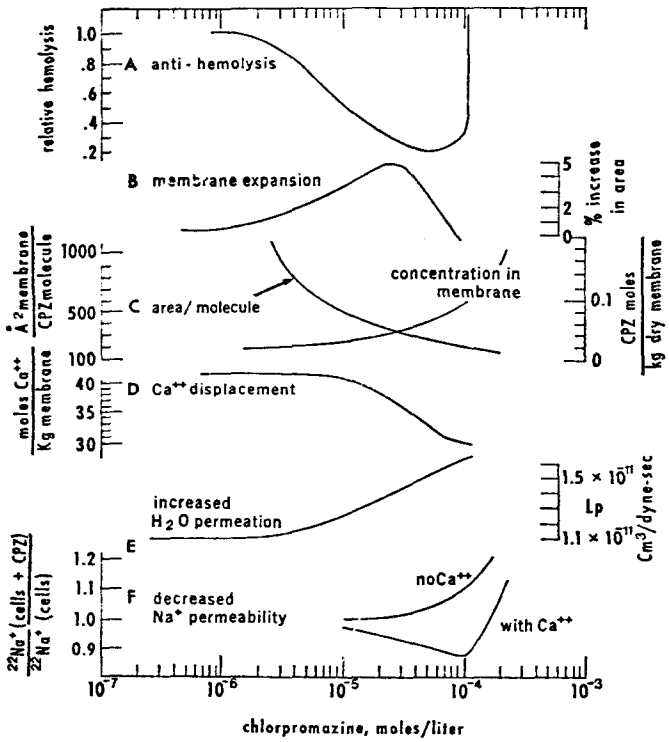

FIG. 2. A summary of the membrane actions of chlorpromazine. A, chlorpromazine protects human erythrocytes from osmotic hemolysis (350, 511, 556). B, membrane area expansion of spherical erythrocyte ghosts by CPZ (550), showing that about 2% expansion occurs at concentrations which cause local anesthesia (10^{-5} M). C, the membrane concentration of CPZ (scale on right), and the amount of erythrocyte membrane area per single molecule of CPZ (scale on left) (346). D, CPZ displaces membrane-bound Ca^{++} (347). E, CPZ increases the hydraulic permeability coefficient, L_p, of the erythrocyte membrane (555). F, CPZ decreases passive influx of $^{22}Na^+$ into erythrocytes *in the presence of* Ca^{++}; in the absence of Ca^{++} the tranquilizer increases the passive permeability (549). High sublytic concentrations of CPZ overexpand the membrane, which then buckles inward (invaginates; 540, 544), the cells showing apparently less expansion than really exists. This explains why the peak expansion does not exactly match the peak of protection. The experimental points have been omitted for sake of clarity.

Current evidence indicates that tetrodotoxin competes with Na^+ for sites on human erythrocyte membranes (590d), but no specific binding has been found for bovine erythrocyte membranes (244b).

2) The concentrations of these anesthetics and tranquilizers which cause 50% antihemolysis are identical to the nerve-blocking concentrations (frog sciatic nerve) as summarized in figure 4 (539–542, 544, 545, 548, 552, 554, 556).

3) The cationic form of the amine anesthetics (*e.g.*, chlorpromazine) is active on both erythrocyte and nerve membranes (542, 548), although the neutral form is also active.

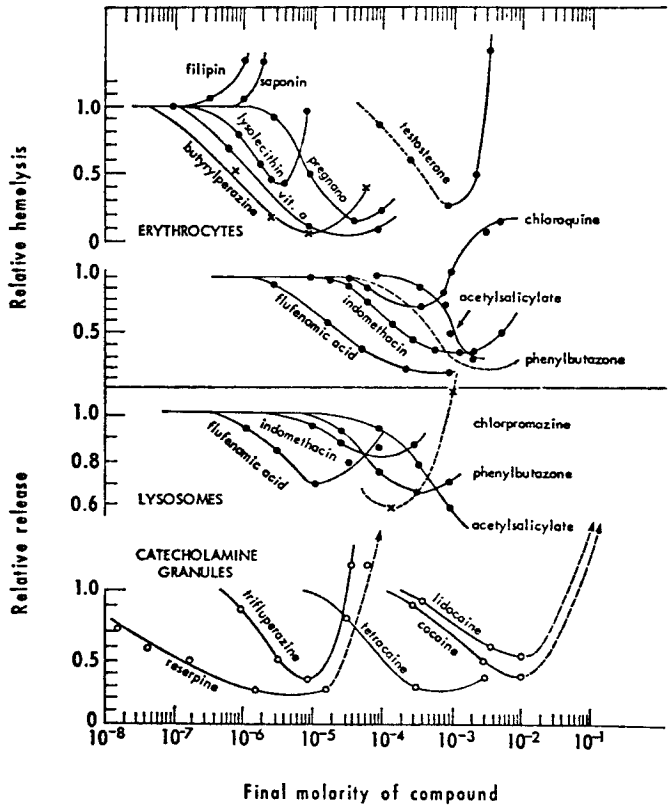

FIG. 3. The general property of membrane protection by lipid-soluble drugs. Low concentrations of these compounds (tranquilizers, vitamin A, pregnanolone, *etc.*), including the anti-inflammatory compounds (adapted from 291), protect human erythrocytes from osmotic hemolysis; the cholesterol-specific compounds (filipin, saponin) only produce lysis. These compounds show a similar order of potency in reducing the release of acid hydrolases from lysosomes (adapted from 241, 607). Low concentrations of the anesthetics and tranquilizers reduce spontaneous release of noradrenaline from catecholamine granules (adapted from 187a–187e, 652b). High concentrations of almost all these compounds disrupt the membranes.

4) High and lytic concentrations irreversibly damage both excitable and inexcitable membranes (542).

5) Anesthetics expand both nerve-lipid-monolayers (578, 579) and erythrocyte membranes (382, 510, 544, 548, 550–552). Under conditions of general anesthesia the erythrocyte membrane expands by approximately 0.4% in surface area (552), which is the same as the value predicted by other workers on the basis of pressure reversal of general anesthesia (367).

6) The membrane/buffer partition coefficients of anesthetics in erythrocyte membranes are similar to the coefficients in excitable membranes (511).

Tables 2 to 5 list the nerve-blocking concentrations and the membrane/buffer partition coefficients for 70 anesthetics. The membrane/buffer partition coeffi-

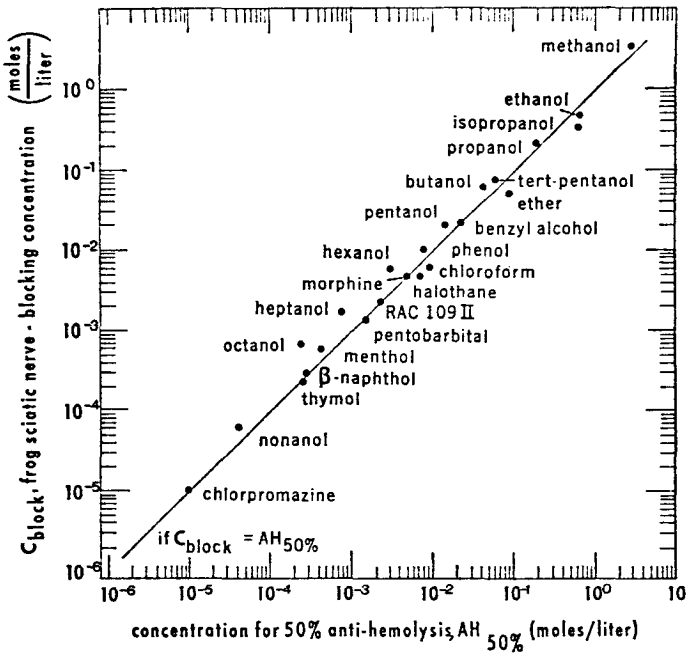

FIG. 4. Illustrating the correlation between the nerve-blocking drug concentrations (minimum blocking concentrations for inhibiting conduction in frog sciatic nerve) and the concentrations which protect human erythrocytes by 50% (see table 5).

cients for anesthetics other than those listed may be extrapolated from the relation between $P_{m/b}$ and the olive oil/water partition coefficient (fig. 5) or $P_{m/b}$ and the octanol/water partition coefficient (fig. 6).

The membrane/buffer partition coefficients of anesthetics in erythrocyte membranes are virtually the same as those in excitable membranes (see fig. 7; 511).

From all these data the membrane concentrations of the anesthetics are calculated and these are summarized in figure 8. From inspection of table 5 and figure 8 it is apparent that the membrane concentrations do have a moderate range of variation, from a high value of 0.259 moles/kg dry membrane for N_2, down to a low value of 0.006 moles/kg for RAC 109 (a local anesthetic amine; 512), a range of 43-fold. It appears, therefore, that the Meyer-Overton rule of anesthesia is approximately correct, but does not hold rigorously, despite the fact that there is an excellent correlation between the nerve-blocking concentrations and the membrane/buffer partition coefficients (see fig. 9).

The data for the membrane concentrations can be used to test various hypotheses of anesthesia. At least three modifications to the Meyer-Overton rule have been proposed:

1) Benson and King (49), as well as Pauling (471) and Miller (411, 412) have postulated that the molecular polarizability is important in determining potency, controlling the anesthetic's association with membrane components (49) or with membrane water (411, 471).

TABLE 2

The sciatic nerve-blocking concentrations for inhalational anesthetics

	Sciatic Nerve-blocking Concentration			Sciatic Nerve-blocking Concentration	Water/gas Solubility Coefficient (from table 3)	Sciatic Nerve-blocking Concentration
	Atmospheres	Species	Ref.			
				moles/l gas		*moles/l H_2O*
Ne	578	Frog 22°	232	23.7	.011	.26
Ar	163	Frog 22°	232	6.68	.0340	.227
	325	Rat 37°	104			
Kr	54.5	Frog 22°	232	2.24	.059	.132
	~45	Rat 37°	104			
Xe	13.6	Frog 22°	232	.557	.117	.0652
	~10	Rat 37°	104			
N_2	~143	Frog 22°	232	5.86	.0149	.0875
CH_4	101	Rat 37°	104	4.04	.0334	.135
N_2O	13.6	Frog 22°	232	.557	.230	.128
	11.5	Rat 37°	105	.47	.439	.20
C_2H_4	11.2	Rat 37°	104	.44	.118	.052
c-C_3H_6	1.8	Rat 37°	104	.071	.272	.0193
SF_6	~50	Rat 37°	104	1.97	.0051	.0101
CF_2Cl_2	4.05	Rat 37°	105	.159	.0515	.0082
Difluorethylene	15.5	Rat 37°	105			
Difluorethane	2.0	Rat 37°	105			

2) Mullins (1a, 423–425) predicted that equinarcotic effects should occur at equal volume occupations of anesthetic within the membrane phase, on the basis that large molecules would cause greater perturbations in the membrane than small molecules.

3) Instead of choosing the volume or polarizability of the molecule as an index of the "sphere of influence" of the molecule, Seeman *et al.* (553) considered the ΔF (or free energy of adsorption of the drug to the membrane) as the most general index of the extensive property of the anesthetic in the receptor-drug interaction.

The data summarized in figure 10 indicate that the anesthetizing membrane concentration of a small molecule is higher than that for a bulky anesthetic molecule. Calculation of $C_{membrane} \cdot V_{molecule}$ (fig. 11 and last column of table 5) supports the idea that equinarcotic effects occur at equal volume occupations of the cell membrane. The volume fraction of the membrane occupied by the anesthetic varies from 8.5 ml/kg dry membrane for thymol, down to 1.0 ml/kg for a large phenol, with the single exception of menthol (and also Δ^1-tetrahydrocannabinol, but this was not pure). This 8.5-fold variation in the volume occupation is better than the 43-fold variation in the membrane concentrations. [An analogous dependence on molecular volume is noted in the theory of odors, but in addition there is a dependence on molecular shape (18, 143).]

While the Meyer-Overton-Mullins rule of anesthesia thus receives considerable direct experimental support, it should be pointed out that the parameter $C_{membrane} \cdot \Delta F$ varies even less than $C_{membrane} \cdot V_{molecule}$, and exhibits a con-

TABLE 3

The Bunsen solubilities of inhalational anesthetics*

	Water/Gas†		Olive Oil/Gas	
	22–25°	37°	22–25°	37°
Ne	0.011 (362, 407, 420)	0.0097 (362, 483, 581)	0.0196 (44)	0.0226 (44, 483, 581)
Ar	0.034 (164, 362, 407)	0.028 (362, 581)	0.144 (44, 362)	0.140 (44, 46, 581)
Kr	0.059 (362)	0.0505 (104, 362, 581)	0.44 (362)	0.443 (104, 362, 407, 581)
Xe	0.117 (362, 407)	0.085 (362)	1.9 (362)	1.78 (104, 362, 407, 413)
N_2O	0.230 (73)	0.423 (32, 68, 73, 332, 386, 457, 523, 571, 581)	1.56‡	1.50 (104, 403)
N_2	0.0149 (68, 270, 386,	0.0130 (68, 270, 483, 581)	0.0632 (44, 362, 483)	0.068 (44, 104, 289, 362, 483)
CH_4	0.0334 (407)		0.287‡	0.276 (104, 407)
H_2	0.018 (362)	0.0173 (270, 362, 483, 581)	0.042 (362)	0.05 (362, 483, 581)
C=O	0.0228 (270, 386, 483)	0.0184 (270, 362, 483)	0.0893 (44, 483)	0.0914 (44, 483)
C_2H_4	0.1182 (407)	0.081 (240)	1.31‡	1.262 (104, 407, 523)
c—C_3H_6	0.272 (173, 499, 523)	0.208 (457, 523)	15.74 (523)	11.53 (68, 523)
SF_6	0.0051‡	0.0049 (102, 377, 407, 483, 581)	0.268‡	0.258 (104, 170, 407, 413, 483, 581)
CF_2Cl_2	0.0515 (407)		5.15‡	4.94 (104, 407)
$CHCl_3$	6.8 (403, 442)	3.92 (32, 442)	276‡	265 (403)
Cl_2C=CCHCl	1.61‡	1.55 (482)	998‡	960 (173)
Ether	25 (32)	13.8 (32, 102, 245, 361, 362)	68‡	64.8 (174)
Halothane	1.5 (32)	0.807 (360, 523)	370 (173)	224 (360)
Methoxyflurane		4.5 (245)		970 (173)
Fluroxene	~0.87‡	0.84 (538a)	~50‡	47.7 (173)

* Averaged from refs. cited in brackets. Solubility is in volumes of anesthetic gas dissolved in 1 volume of liquid at 760 mm.

† The saline/gas partition coefficients are generally lower; *e.g.*, water/gas coefficient for halothane is 0.74 while the saline/gas coefficient is 0.70 (ref. 360).

‡ Calculated by multiplying the partition coefficient at 37° by 310/298.

stant value of about 60 calories per kg of membrane for each alcohol anesthetic. In order to substantiate this free energy hypothesis it will be necessary to obtain the free energies of adsorption for all the anesthetics, there only being reliable data for the alcohols (553), chlorpromazine (346) and some phenols (382). The

TABLE 4

Relation between (membrane/water) and (oil/water) partition coefficients

	Membrane/ Gas, 37° (ref. 483)	Membrane/ Gas, 25°	Membrane/ Water, 37° #	Membrane/ Water, 25°	Octanol/ Water, 25° (ref. 364)	Olive Oil/ Water, 37° (from table 3)	Oil/Water, 25° (from table 3)
C═O	.094	.044 (483)	5.06	2.02*		4.98	3.92
Ne	.012	.0056†	1.19	.496*		2.33	1.78
N_2	.096	.044†	7.4	2.94*		5.23	4.24
CH_4				.632‡	3.16		8.6
H_2	.024	.011†	1.39	.61*		2.90	2.34
C_2H_4				1.0‡	5.01	14.4§	11.1
c-C_3H_6				3.17‡	15.85	34.4§	~34§
CF_4				5.25‡	26.3	17.0	15.8
SF_6	.151	.069†	30.8	13.5*	43.6	52.7	52.7
				8.8‡			
CF_2Cl_2				8.4‡	41.7		100
$CHCl_3$				18.7‡	93.5	84‖	63‖
Trichlor-ethylene				39‡	195		400§
Ether				1.18‡	5.9	4.6	2.7¶
Halothane				12.9‡	64.5	278	246
Methoxy-flurane				32.4‡	162	216	216

* Calculated by dividing the membrane/gas partition coefficient (at 25°) of column 2 by the average water/gas partition coefficient (at 25°) in table 3.

† Extrapolated from the value at 37° (shown in column 1) by multiplying by 0.46, where 0.46 is the ratio of the membrane/gas partition coefficients at 37° and 25° for C═O (ref. 483).

‡ Obtained by dividing the octanol/water partition coefficient (in column 5) by 5.

§ Ref. 538a.

‖ Average value from table 3 and ref. 538a.

¶ *Cf.* value of 2.4 reported by ref. 404.

Obtained by dividing the membrane/gas partition coefficient at 37° (column 1) by the average water/gas partition coefficient at 37° (table 3).

free energy of binding, ΔF, is obtained by the relation $\Delta F = -RT \ln K$, where K is the affinity constant, measured experimentally by carrying out an adsorption isotherm over a wide range of anesthetic concentrations (553).

A. Summary of membrane concentration data for local anesthesia

The data reviewed in figure 8 and table 5, therefore, indicate that the local anesthetic blocking concentration within the frog sciatic nerve membrane is of the order of 0.04 moles per kg dry membrane. This is equivalent to about 250,000 molecules per square micron, or approximately 400 A^2 of membrane per anesthetic molecule. The average volume occupation of the membrane is 0.3% under conditions of local anesthesia (fig. 11).

At very high anesthetic concentrations, when all the anesthetic sites are saturated, the membrane concentration is of the order of 0.065 moles per kg dry

TABLE 5

The membrane concentrations of anesthetics

	Nerve Blocking Concentration* C_{block}	Concentration for 50% Anti-hemolysis $AH_{50\%}$	Membrane/Buffer Partition Coefficient† [refs. 511, 553] P	Anesthetic Concentration in Membrane† $C_{membrane}$	Molecular Volume V_{mol}, (ref. 71)	Volume of Anesthetic in Membrane‡ $C_{mem} \times V_{mol}$
	moles/l H_2O	*moles/l H_2O§*		*moles/kg dry mem*		*ml/kg membrane*
H_2	4.2×10^{-1}‖		0.61¶	.256	7.0	1.8
1. Ne	2.68×10^{-1}**		0.496¶	.133	9.3	1.2
2. Ar	2.16×10^{-1}**		0.9††	.194	10.9	2.1
3. Kr	1.24×10^{-1}**		1.6††	.198	11.1	2.2
4. Xe	5.73×10^{-2}**		3.0††	.172	20.2	3.5
5. N_2	8.8×10^{-2}**		2.94¶	.259	15.8	4.1
6. CH_4	1.35×10^{-1}**		0.632¶	.085	17.1	1.5
7. N_2O	1.28×10^{-1}**		0.62††	.080	18.9	1.5
8. C_2H_4	5.2×10^{-2}**		1.0¶	.052	23.9	1.2
9. c-C_3H_6	1.93×10^{-2}**		3.17¶	.061	29.6	1.8
10. SF_6	1.01×10^{-2}**		8.75¶	.088	45.1	4.0
11. CF_2Cl_2	8.2×10^{-2}**		8.35¶	.069	43.7	3.0
12. Benzyl alcohol	2.0×10^{-2}§	2.2×10^{-2}	4.0§	.080	64.1	5.1
13. Methanol	2.4§	~2.7	0.045‡‡	.108	21.7	2.3
14. Ethanol	5.0×10^{-1}§	6×10^{-1}	0.14‡‡	.070	31.9	2.2
15. Propanol	2.18×10^{-1} (579)	1.9×10^{-1}	0.45‡‡	.098	42.2	4.1
16. Butanol	6.8×10^{-2} (579)	4.2×10^{-2}	1.5‡‡	.102	52.4	5.3
17. Pentanol	2.1×10^{-2} (579)	1.45×10^{-2}	3.6§	.075	62.6	4.7
18. Hexanol	6×10^{-3}§	3.00×10^{-3}	13.0§	.039	72.9	2.9
19. Heptanol	1.75×10^{-3}§	7.50×10^{-4}	39.6§	.030	83.1	2.4
20. Octanol		2.35×10^{-4}	151.8§	.036	93.3	3.3
21. Nonanol	6.4×10^{-4}§	4.1×10^{-4}	582§	.024	104	2.5
22. Decanol		1.0×10^{-5}	1222§	.012	114	1.4
23. Isopropanol	3.51×10^{-1} (579)	4×10^{-1}	0.276‡‡	.097	42.2	4.1
24. Tert-amyl alcohol	8.1×10^{-2} (579)	6×10^{-2}	1.55‡‡	.125	62.6	7.8
25. Menthol	5.8×10^{-4} (579)	5×10^{-4}	200‡‡	.116	105.7	12.2
26. Thymol	2.2×10^{-4} (579)	2.6×10^{-4}	400‡‡	.088	96.6	8.5
27. β-Naphthol	3.0×10^{-4} (579)	2.4×10^{-4}	138‡‡	.042	79.5	3.3
28. Phenol	7×10^{-3}§	7.8×10^{-3}	8.5§	.060	46	2.7
29. Chloroform	5×10^{-3}§	9×10^{-3}	18.7‡‡	.112	41.6	4.6
30. Diethylether	5×10^{-2}§	9×10^{-3}	1.18‡‡	.059	53	3.1
31. Halothane	5×10^{-3}§	8×10^{-3}	12.9‡‡	.065	53.3	3.4
32. Urethane	2.25×10^{-1} (631)		0.57§	.128	49.6	6.3
33. Pyridine	5.9×10^{-2}§§		0.9‡‡	.053	44.3	2.3
34. Aniline	2.0×10^{-2}§§		1.59‡‡	.032	56.4	1.8
35. Nitrobenzene	2.95×10^{-2}§§		14.2‡‡	.042	62.6	2.6
36. Acetanilide	1.5×10^{-2}§§		2.9‡‡	.044	79.0	3.4
37. Quinoline	2.0×10^{-2}§§		21.4‡‡	.043	70.2	3.0
38. Hydroquinone	2.5×10^{-2}§§		0.78‡‡	.020	57.8	1.2
39. Antipyrine	6.0×10^{-2}§§		0.34‡‡	.024	107.1	2.6
40. 4-QCH_3-phenol		6×10^{-3}	5.4‡‡	.033	61	2.0
41. 4-F-phenol		3×10^{-3}	13.1‡‡	.039	49	1.9
42. 3-$N(CH_3)_2$-phenol		2.8×10^{-3}	8.0‡‡	.022	75	1.7
43. 4-CO_2CH_3-phenol		2.4×10^{-3}	18.1‡‡	.044	75	3.3
44. 3-NO_2-phenol		2.2×10^{-3}	20‡‡	.045	60	2.7
45. 3-CH_3-phenol		1.7×10^{-3}	17.7‡‡	.030	57	1.7
46. 4-OC_2H_5-phenol		1.6×10^{-3}	13.1‡‡	.021	71	1.5
47. 4-CH_3-phenol		1.4×10^{-3}	17.7‡‡	.025	57	1.4
48. 2-Cl-phenol		1.15×10^{-3}	28.8‡‡	.033	55	1.8
49. 2,6-$(CH_3)_2$-phenol		1.05×10^{-3}	44‡‡	.046	68	3.2
50. 3,5-$(CH_3)_2$-phenol		9.5×10^{-4}	43‡‡	.041	68	2.8
51. 4-Cl-phenol		7.4×10^{-4}	43‡‡	.032	55	1.8
52. 2-CF_3-phenol		5.5×10^{-4}	119‡‡	.066	65	4.3
53. 4-Br-phenol		3.6×10^{-4}	92§	.033	58	1.9
54. 2,4-Cl_2-phenol		2×10^{-4}	375‡‡	.075	65	4.9
55. 3-I-phenol		1.9×10^{-4}	188‡‡	.036	63	2.3
56. 4-t-C_4H_9-phenol		1.27×10^{-4}	164‡‡	.021	88	1.8
57. 3-CH_3,4-Cl-phenol		1.13×10^{-4}	131§	.015	67	1.0
58. Procaine	4.6×10^{-3} (573)	‖‖	3.1 (575)	.014	142	2.0
59. Cocaine	2.6×10^{-3} (573)		15.7 (575)	.041	163	6.7
60. Tropacocaine	2.2×10^{-3} (573)		20.4 (575)	.045	134	6.0

TABLE 5—*Continued*

	Nerve Blocking Concentration* C_{block}	Concentration for 50% Anti-hemolysis $AH_{50\%}$	Membrane/Buffer Partition Coefficient‡ [ref. 511, 553] P	Anesthetic concentration in Membrane‡ $C_{membrane}$	Molecular Volume V_{mol}, (ref. 71)	Volume of Anesthetic in Membrane‡ $C_{mem} \times V_{mol}$
	moles/l H_2O	*moles/l H_2O*		*moles/kg dry mem*		*ml/kg membrane*
61. Chlorpromazine	1×10^{-4}§	1×10^{-5}	1600§	.016	354	2.6
62. RAC 109 I	8×10^{-4} (13)	2.73×10^{-3}	8§	.006	204	1.3
63. RAC 109 II	2.3×10^{-3} (13)	2.37×10^{-3}	8§	.018	204	3.7
64. Morphine	5.5×10^{-3}§	5.2×10^{-3}	2.7§	.015	145	2.2
65. Methadone	$2\text{-}3 \times 10^{-4}$§		32§	~.010	193	~2.0
66. Pentobarbital	1.7×10^{-4}§	1.6×10^{-3}	9.6§	.016	133	2.2
67. Diphenylhydantoin	8.3×10^{-4}§	1.5×10^{-3}	40§	.035	136	4.8
68. Barbital	28×10^{-3}§		0.68§	.019	102	1.9
69. Phenobarbital	5.7×10^{-4}§		6.40§	.036	124	4.5
70. THC¶¶		1×10^{-5}	~340§	~.0034	210	~0.7

* Frog sciatic nerve (22°).

† Determined experimentally at C_{block} (or at $AH_{50\%}$) and in presence of 0.9% NaCl (22°). P has units of [(moles/kg membrane)/(moles/l H_2O)].

‡ Refers to excitable membrane ($C_{membrane} = P \cdot C_{block}$).

§ Determined experimentally in this laboratory.

‖ H_3 is ¼ potency of N_3 (ref. 79); estimated C_{block} = 572 atm.

¶ See table 4.

** See table 2.

†† Estimated from the oil/water partition coefficient (table 3) with relation in figure 5.

‡‡ Obtained by dividing the octanol/H_2O partition coefficient by 5 (see refs. 253, 366, 511).

§§ Frog sartorius muscle (ref. 5).

‖‖ AH_{50} values for anesthetic esters are higher than C_{block}, presumably because of the high activity of erythrocyte membrane cholinesterase.

¶¶ Δ^1-Tetrahydrohydrocannabinol (117) rat, pH 7.4.

membrane for the anesthetic alcohols (553) and 0.08 moles per kg for chlorpromazine (346). An example of the membrane concentration for chlorpromazine is shown in figure 2C. These high membrane concentrations of anesthetics, which correspond to around one anesthetic molecule per five phospholipid molecules, are invariably associated with the threshold for membrane lysis (129).

The figure of 250,000 lipid-soluble anesthetic molecules per square micron of membrane compares with ~10 to 100 tetrodotoxin binding sites/μ^2 on various nerve cells (129a, 244b, 327a, 417). (It has been suggested that membrane cholesterol may be the receptor for tetrodotoxin (642a); this appears unlikely since cell membranes generally have about 10^8 cholesterol molecules/μ^2.)

B. Membrane concentration data for general anesthesia

It is known that the anesthetic concentrations (in the aqueous phase) required for general anesthesia are of the order of $\frac{1}{10}$ to $\frac{1}{20}$ the concentrations required for local anesthetic block (see later section). On this basis, therefore, the membrane anesthetizing concentrations (under conditions of general anesthesia) will also be about $\frac{1}{10}$ to $\frac{1}{20}$ of those found for local anesthesia (*i.e.*, of those listed in table 5). This is because the membrane/buffer partition coefficients for neutral anesthetics are independent of the aqueous concentration of the anesthetic. The membrane concentrations are tabulated in table 6.

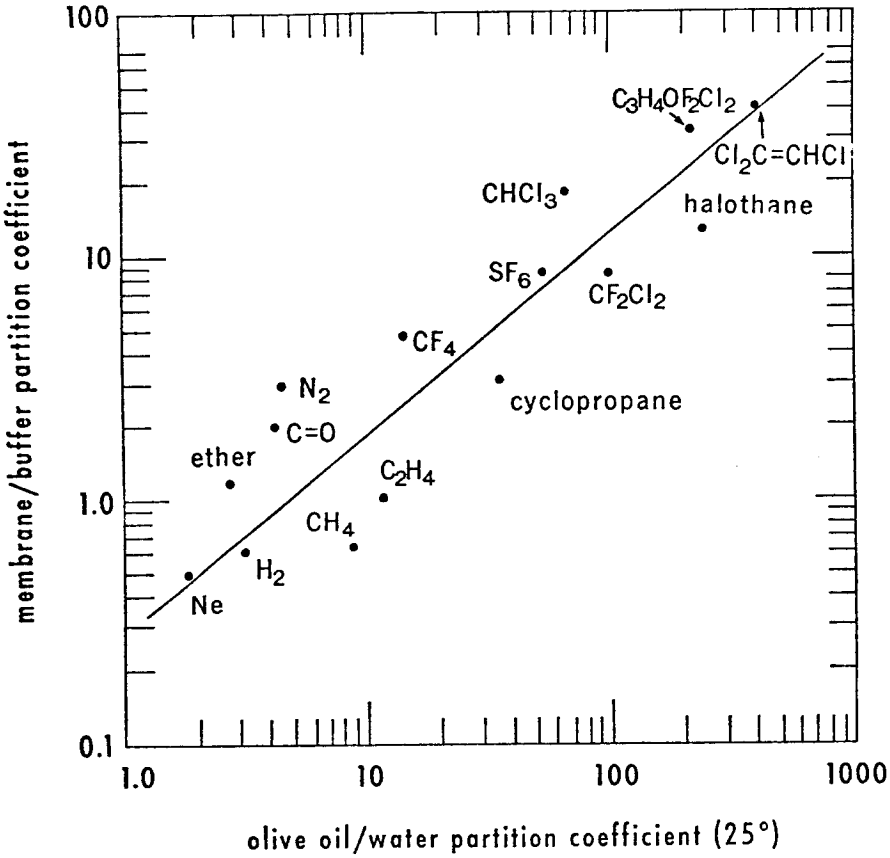

FIG. 5. Showing the correlation between the membrane/buffer partition coefficients and the olive oil/water partition coefficients for a variety of gaseous and volatile anesthetics (at 25°C) (from tables 3, 4).

Historically, the anesthetizing concentration in the membrane phase, *under conditions of general anesthesia*, had been predicted as being 0.05 moles/liter olive oil, on the basis that the membrane had the same composition as olive oil (24, 399–404, 461). Experimentally, in fact, the membrane/buffer partition coefficients are about 1/7 to 1/15 lower than the oil/water coefficients (fig. 5). The volumes of anesthetic occupying the membrane are also lower, therefore, by a factor of 7- to 15-fold, as shown in the few examples in table 7.

The importance of these anesthetic volume occupations (listed in tables 5 and 7) will become apparent in a later section, where it is shown that the volume expansion of the membrane observed experimentally is of the order of 10 times greater than the anesthetic volume of occupation for both general and local anesthesia.

C. Forces controlling the anesthetic binding to the membrane

It has been demonstrated that the narcotic activity of anesthetics correlates much better with the non-aqueous/aqueous partition coefficient than with any

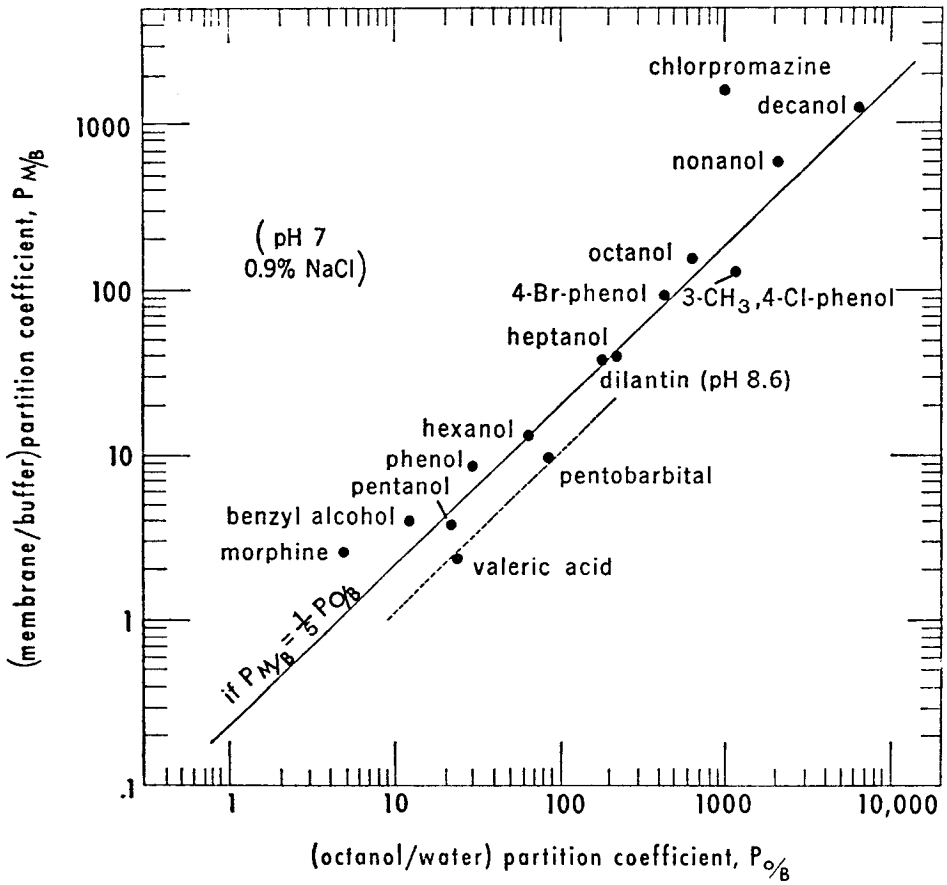

FIG. 6. Illustrating that the membrane/buffer partition coefficients of various anesthetics (at 25°C, and in the presence of 0.9% NaCl, pH 7) are about 1/5 of the octanol/water partition coefficients. The correlation between the coefficients for the negative anesthetics seems to be slightly different, but this may not be significant.

other parameter of the anesthetic molecule, such as polarizability, molecular weight, or molar attraction constant (187, 366, 407, 408, 522). The general correlation between narcotic potency and partition coefficient now extends to the membrane/buffer partition coefficient as well, as indicated by the data summarized in figure 10.

The correlations of anesthetic potency to the non-aqueous/aqueous partition coefficient have supported the classical idea that the membrane anesthetic interaction is hydrophobic in nature (382, 532, 553). More direct evidence indicating that the anesthetic is partly or completely surrounded by hydrophobic components of the membrane comes from data which measure the free energy of adsorption of the anesthetic to the membrane (346, 382, 511, 532, 553). The free energy of adsorption of alcohols to erythrocyte membranes is −695 calories per mole of $-CH_2$ groups. This suggests that the methylene groups of the alcohol reside in some hydrophobic region of the membrane, on the basis that −700 to

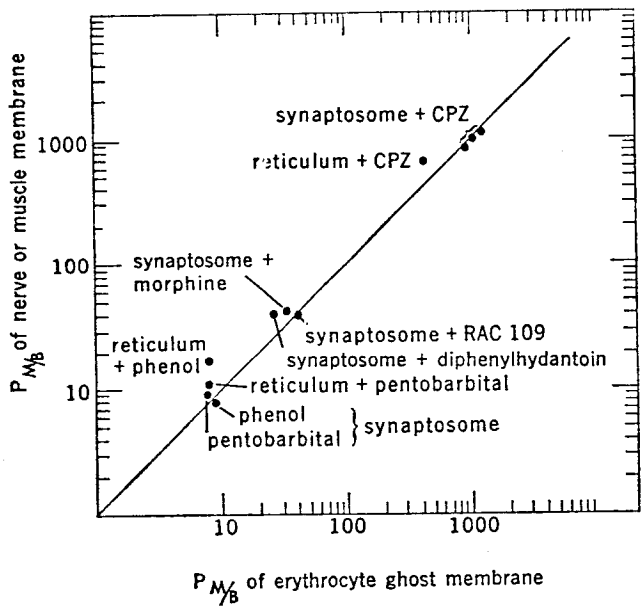

FIG. 7. Illustrating that the membrane/buffer partition coefficients of anesthetics in nerve and muscle membranes are the same as those for erythrocyte membranes. The CPZ concentrations ranged from 0.07 to 0.2 mM. The phenol, pentobarbital, morphine, RAC 109 and diphenylhydantoin concentrations were 6.5, 0.18, 5.2, 2.7 and 0.8 mM, respectively.

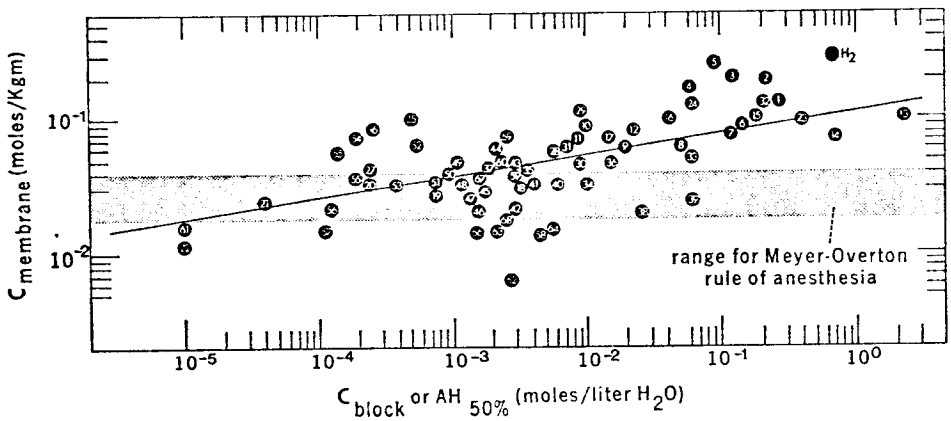

FIG. 8. Illustrating that the membrane concentrations of anesthetics (for equal nerve-blocking or antihemolytic effects) are approximately but not exactly predicted by the Meyer-Overton rule of anesthesia. See table 5 for code to drugs.

−800 cals/mole is the work involved in transferring one $-CH_2$ group from an aqueous phase to a completely non-polar phase (532). The hydrophobic region may consist of 1) non-polar portions of lipid molecules; 2) the non-polar interfaces between lipid and protein molecules; or 3) the hydrophobic regions of protein molecules.

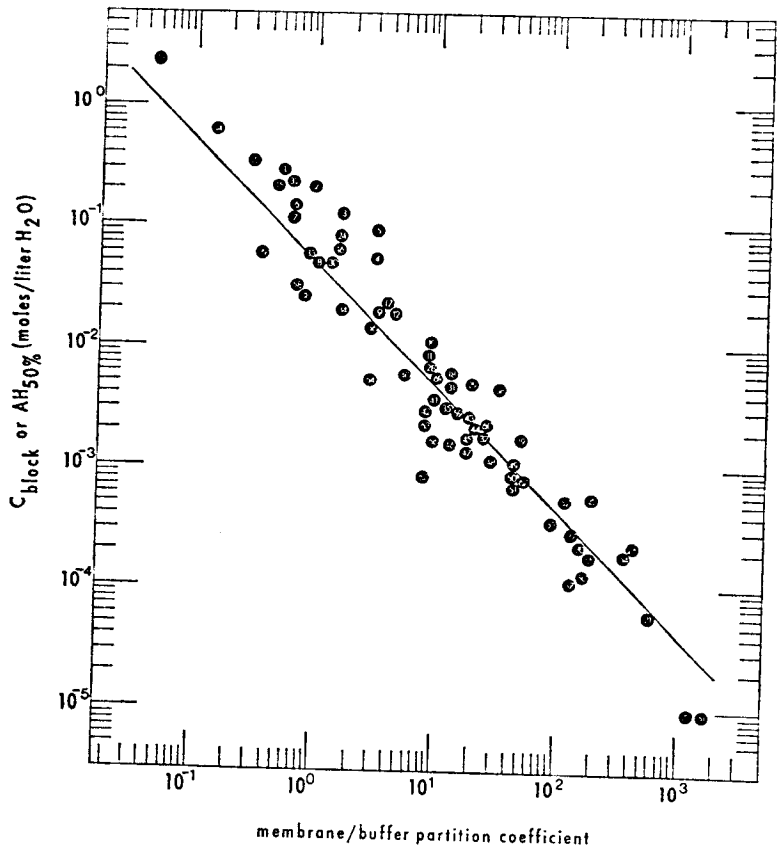

FIG. 9. Showing that the nerve-blocking (or antihemolytic) concentration of an anesthetic directly correlates with the membrane/buffer partition coefficient. See table 5 for code to anesthetics.

The ΔF of anesthetics adsorbing to proteins is generally in the region between -100 and -560 calories per mole of $-CH_2$, although higher values of -650 to -1100 occur with proteins which may undergo conformation changes (532). Thus, the membrane site is probably the non-polar portion of lipid molecules or involves a protein which undergoes a conformation change on binding the alcohol.

The interaction of chlorpromazine with the membrane is also hydrophobic as indicated by a ΔF of -9400 cals/mole chlorpromazine, and by a negative enthalpy of adsorption ($-\Delta H$) which becomes more negative at higher temperatures (37, 346).

The data for the energy of anesthetic binding thus indicate that the nearest neighbors to the anesthetic molecule within the membrane are hydrophobic moieties, rather than being water molecules or water clathrates (471).

The binding or adsorption of anesthetics to membranes appears to depend on the following factors:

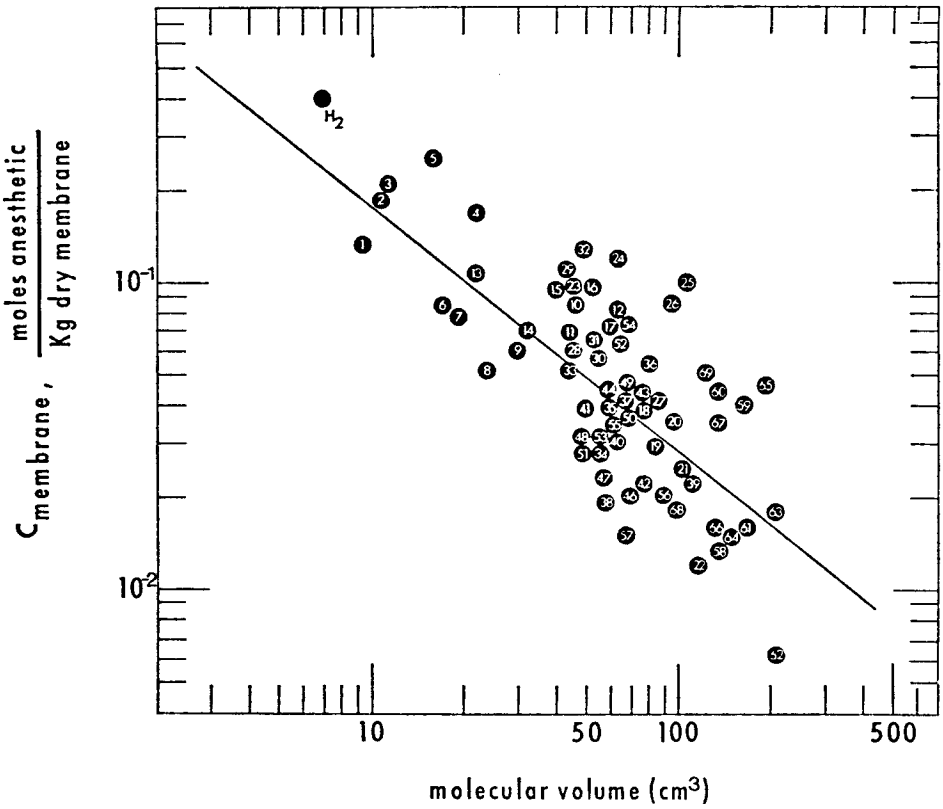

FIG. 10. The anesthetic concentration (for nerve-block) in the membrane phase (ordinate) is lower for larger molecules, as predicted by the Mullins' rule of anesthesia (423). See table 5 for code to anesthetics.

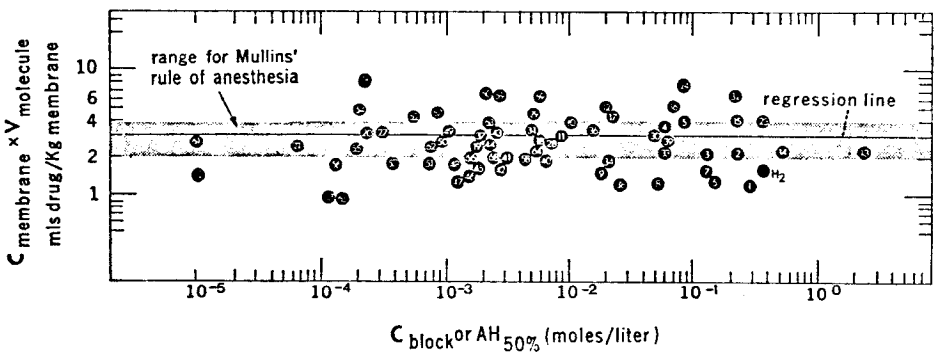

FIG. 11. The occupying volume of the anesthetic (for nerve-block) in the membrane phase (ordinate) has a constant value of about 3 ml per kg dry membrane, or 0.3%, for all the anesthetics. Although this generalization fits Mullins' rule (423), the observed expansion of the membrane volume (or area) is actually about 10 times this amount, as explained in the text.

TABLE 6

	General Anesthesia	Local Anesthesia
Anesthetizing concentrations within the membrane	~0.003 moles/kg dry membrane = 20,000 molecules/μ^3	0.04 moles/kg dry membrane = 250,000 molecules/μ^3
Anesthetizing volume occupation within the membrane	~.02 mls/100 g dry membrane (or ~0.02% v/v)	0.3 mls/100 g dry membrane (or ~0.3% v/v)
Anesthetic sites at saturation	0.07 moles/kg dry membrane = 500,000 molecules/μ^2	

TABLE 7

A comparison of the anesthetic volume occupations in oil versus those in the membrane

	Under Conditions of General Anesthesia (Rat; ref. 104)		Under Conditions of Local Anesthesia (Rat Sciatic Nerve; ref. 104)	
	Anesthetic volume in		Anesthetic volume in	
	Olive oil (ml drug/100 g oil)	Membrane (ml drug/100 g membrane)	Olive oil (ml drug/100 g oil)	Membrane (ml drug/100 g membrane)
Xenon	.025*	.003†	.5*	.07†
N_2O	.23*	.03†	4.5*	.6†
N_2O	.055‡	.008†	1.1§	.15‖
Cyclopropane	.05‡	.005†	2.0§	.18‖
Ethylene	.058‡	.005†	1.4§	.12‖
Methane	.057‡	.004†	2.0§	.15‖
Argon	.055‡	.008†	1.4§	.21‖

* Obtained by direct measurement experimentally (538).

† Calculated from the anesthetic volume occupation in oil and by using figure 5.

‡ Calculated from the anesthetic concentration in the vapor phase (104) and the anesthetic solubility in oil (table 3).

§ Calculated from the anesthetic volume occupation in the membrane, and by using figure 5.

‖ From table 5.

1) Partition coefficient in a non-aqueous/aqueous system, as already discussed.

2) The charge distribution on the anesthetic (90). The anesthetic potencies, however, correlate poorly with sigma or Hammett constants (253, 532).

3) The molecular weight or volume, as already discussed.

4) *pH.* Increasing the pH markedly increases the membrane/buffer partition coefficient of procaine (575) or of chlorpromazine (346). There are insufficient data for neutral anesthetics.

5) *Temperature.* The membrane binding of alcohols (129, 545) increases with temperature, while that for chlorpromazine decreases slightly with temperature (346).

6) *Content of membrane cholesterol.* Cholesterol depletion of liver membranes increases the binding of polar steroids (dexamethasone, hydrocortisone, corticos-

terone) while reducing the binding of more hydrophobic steroids (deoxycorticosterone, progesterone, testosterone, diethylstilbestrol) (235). The presence of cholesterol in phospholipid membranes lowers the membrane/buffer partition coefficient of hydrocortisone, deoxycorticosterone, estrone and progesterone (582).

7) *Ionic strength.* The membrane/buffer partition coefficients of the anesthetic amines become lower as the NaCl concentration is increased (511, 512); those for the negatively charged anesthetics (barbiturates, fatty acids, hydantoins) increase with increased NaCl.

8) *Anesthetic concentration.* The membrane/buffer partition coefficients of neutral anesthetics are approximately constant and independent of the anesthetic concentration in the anesthetizing range (129, 382, 398, 553). At higher sublytic and lytic concentrations these neutral drugs increase the partition coefficient (129, 398). The partition coefficients of the amine anesthetics, however, are practically always dependent on the free concentration of the anesthetic; the coefficients tend to fall markedly as the free concentration rises (346, 511).

9) *Ca^{++} concentration.* Unpublished work in this laboratory has shown that increasing the free Ca^{++} can displace membrane-adsorbed chlorpromazine, in the same way as free chlorpromazine displaces membrane-bound Ca^{++} (347). No work has been done on whether free Ca^{++} can alter the membrane-bound levels of neutral anesthetics; it is known that neutral anesthetics can increase the concentration of membrane-bound Ca^{++} (547).

10) *Reversibility of binding.* In general, the binding of anesthetics to membranes is reversible (74, 349, 556). High concentrations of anesthetics, however, irreversibly expose new binding sites in the membrane, and the membrane/buffer partition coefficient rises sharply (129, 398). For some drugs, such as reserpine, there is evidence for persistent binding (444).

11) *Nature of membrane lipids.* Hydrogenation of lipids markedly reduces the binding of chlorpromazine and other amine anesthetics for endoplasmic reticulum membranes (36, 37).

III. The General Property of Membrane Protection by Anesthetics and Tranquilizers

Many lipid-soluble drugs at low concentration protect cell membranes and subcellular membranes. The term "membrane stabilization" was introduced by Guttman (242a) in 1940, who found that Ca^{++} or Mg^{++} prevented or stabilized the resting potential of the nerve membrane from depolarization by potassium or by veratrine. In 1958 Shanes (561) broadened this idea of membrane stabilizers to include any compound which inhibited a change in the membrane resting potential.

The idea of membrane electrical stabilization by drugs can be extended further to include the membrane-protective action of lipid-soluble drugs (542, 544). The general observation is that low concentrations (usually from 10^{-8} to 10^{-3} M) of these lipid-soluble or surface-active compounds protect the membrane from osmotic, mechanical or acid lysis, but that higher concentrations (usually above 10^{-4} or 10^{-3}) are directly and immediately lytic to the membrane.

Examples of this general phenomenon are shown in figure 3. The top half of figure 3 indicates that erythrocytes are protected from osmotic hemolysis by low concentrations of steroids (testosterone, pregnanolone) (3, 539), tranquilizers (butyrylperazine) (113, 211, 527a, 556), phospholipids (lysolecithin), fat-soluble vitamins (vitamin A) and anti-inflammatory compounds (flufenamic acid, indomethacin, phenylbutazone, chloroquine and sodium acetylsalicylate). The value of 1.0 on the ordinate represents approximately 50% hemolysis that occurs in the absence of any drug. The results dealing with the anti-inflammatory compounds have been adapted from Inglot and Wolna (291).

Since virtually all of these compounds are surface active (45a, 92, 329, 468, 542, 546, 574, 641, 668–670), with the possible exception of acetylsalicylate, high concentrations cause lysis. The dose-response curves, therefore, are generally biphasic in shape, as a function of drug concentration. Cholesterol-specific agents, such as saponin and filipin, do not stabilize membranes at any concentration but extract the membrane cholesterol, thereby lysing the cell (543). (The use of a hypotonic saline test medium as shown in figure 3, therefore, is convenient for distinguishing between "specific" hemolysins, which lyse by specifically extracting cholesterol, from those "non-specific" hemolysins which lyse by over-expanding the membrane or by making the cell leaky to monovalent ions, thus inducing a secondary colloid osmotic hemolysis; 479, 480, 541; see 541, 542, 556 for further refs.)

The membranes of the subcellular organelles are also stabilized or protected by low concentrations of these same drugs. Figure 3 shows that the spontaneous release of acid hydrolases from lysosomes is reduced by low concentrations of chlorpromazine (adapted from 241) and by low concentrations of the anti-inflammatory compounds (adapted from 607). These latter results are in qualitative and in almost quantitative agreement with the findings of Inglot and Wolna on the erythrocyte (291).

There is an extensive literature on the protective (stabilizing) as well as lytic (labilizing) effects of lipid-soluble drugs on lysosome membranes (83, 163, 241, 285, 287, 288, 304, 371, 372, 414, 603, 607). The qualitative and quantitative results greatly depend on the manner of preparing the lysosomes, the glassware, ionic strength, pH, temperature, and on the mode of artificial disruption while testing the protective action of the drug. It may also be that the concentration of cholesterol in the different lysosome membranes also differs, and, as mentioned earlier, this is a very significant factor in determining the membrane/buffer partition coefficient; no work has been carried out relating the level of lysosome membrane cholesterol to the lysosome-protecting potency of drugs.

Also shown in figure 3 are some of the observations demonstrating that low concentrations of reserpine, tranquilizers and local anesthetics, all of which are surface-active, reduce the spontaneous loss of catecholamines from catecholamine granules (185–185e, 652b). It appears that all surface-active compounds can cause this general biphasic effect of membrane protection at low concentrations and membrane-lysis at high concentrations.

Membrane actions of anesthetics and tranquilizers have also been found on mitochondria (558, 592, 593) and on platelets (428, 446, 628). The inhibition of

platelet aggregation by anesthetics (628) is particularly interesting because these effects occur at clinical concentrations. The anti-aggregation effects presumably stem from a combined action of the anesthetics on the glycocalyx of the membrane as well as on the basic lipoprotein structure of the membrane.

The toxic effects of high concentrations of the membrane-protective drugs appears to be similar for both the excitable and non-excitable membranes. The nerve membrane becomes depolarized at these high concentrations, and this is presumably related to the fact that practically all these compounds are surface-active and cause membrane disruption.

Pro-lysis (or pre-lysis). In the concentration region between membrane-protection and membrane-disruption there is a concentration zone known as "pro-lytic" or "pre-lytic" (467, 479, 480, 510, 542) wherein the cell becomes very permeable to ions but not to proteins.

IV. Clinical Specificity or Selective Action of Nerve-blocking Drugs

The all-inclusive definition of an anesthetic as a drug which reversibly blocks neurons raises the difficult question of how to explain the clinically apparent specific and selective actions of these drugs. In medical practice, for example, the different phenothiazines and anesthetics are used for different purposes, as anti-histamines, antipruritics, antispasmodics, anticonvulsants, anti-emetics, as anti-motion sickness and antidepressant compounds, tranquilizers, sedatives, for pre-anesthetic medication and as anti-Parkinson's agents (230).

This question becomes particularly cogent upon inspection of the anesthetic membrane-volume occupations in table 5 which demonstrate that nerve block occurs at approximately 3 ml anesthetic per kg dry membrane (0.3 % v/v). This general finding for such a wide variety of chemical compounds *in vitro* would suggest that all these drugs should have a similar action *in vivo*; this is not the case, however.

The purpose of this section is to review some of the reasons which have been proposed to explain the central nervous system (CNS) specificity of these "non-specific" drugs. It seems that one should not stress the neuropharmacological specificity of drugs. Frank and his colleagues (206–208b) have shown that low concentrations of a wide variety of lipid-soluble drugs can anesthetize isolated slabs of cat cerebral cortex (see 207 for further references) as well as suppress motor activity of mice. Rigid classifications of anesthetic and non-anesthetic drugs are difficult to define (see 260, 269, 658).

A. Anesthetic combinations, and anesthetic selectivity arising through "sensitization" effects

Experiments where combinations of anesthetics have been used (137, 162, 207, 208a, 410, 530) generally indicate that there are no special separate mechanisms of action, or special classes of anesthetic. The simplest example is on the lobster axon, where the minimum blocking concentration (MBC) is 8.1 mM for procaine and 35 mM for benzyl alcohol (530); nerve block always occurred whenever the sum of the ratios of the concentration of each anesthetic to its MBC exceeded

unity, indicating that procaine and benzyl alcohol acted in a simple additive way (530). Similar such experiments done for general anesthesia in man (137, 410) or the rat (162) also indicate that simple additive effects are seen between ethylene and halothane, xenon and halothane, N_2O and teflurane, fluroxene and halothane, cyclopropane and teflurane, cyclopropane and halothane. The combination of cyclopropane with ethylene or with N_2O, however, was not additive, there being a small but significant antagonism (162). Non-additive combinations between flurothyl (a convulsant) and various anesthetics have also been described (106a). (See 221b for isobolographic results on combinations of chloral hydrate and ethanol; 649a for combinations of anticonvulsants.)

These combination experiments which are done *in vivo* rely on the very convenient measurement of the minimum alveolar concentration (MAC) of anesthetic required to prevent the animal or man from *moving* in response to tail-clamping in animals or a surgical incision in the case of man (172, 569a). Shim and Andersen (569a) have found, however, that the MAC which prevents response-to-pain is not always the same as the MAC which produces loss of the righting reflex; the ratio between the former MAC and the latter MAC is not the same value for all the anesthetics.

These results (569a) suggest that the anesthetics are producing at least two (or more) effects, the sum of which may differ, depending on the anesthetic or the anesthetic combination employed. In addition to anesthetizing tissues and cells, anesthetics can also cause "sensitization" (547; see later section). Cyclopropane is particularly sensitizing (487), thus counteracting or antagonizing its own anesthetic effects or the anesthetic effects of a second anesthetic (162). If the basis of the sensitization effect is *via* increased neurosecretion (by the direct fluidizing action on the membrane, or by the anesthetic-induced increase in membrane-bound Ca^{++} with an associated increase in stimulus-secretion coupling), different combinations of anesthetics may lead to additive or non-additive effects, depending on the combination of sensitizing and anesthetizing potencies of the drugs.

B. Selectivity arising from differential localization of anesthetics within the CNS

The apparent specificity *in vivo* of some of the nerve-blocking compounds may result from the precise time and space distribution of the drug in various regions of the brain (169, 246, 470). It is otherwise impossible to explain why two structural isomers, which both block nerve conduction (unpublished results in this laboratory), and which have virtually identical physicochemical properties, should produce general anesthesia in one case (hexafluoroisopropyl methyl ether), and convulsions in the other (flurothyl) (334, 335).

A second example wherein selective localization of an anesthetic must be important is that of chlorpromazine. This drug is a potent local anesthetic (133a, 249a, 571a) and suppresses the electrical activity of neurons when applied directly (77, 498a, 507a, 519a, table 5). Since the drug non-selectively blocks neurons directly and stabilizes membranes in a non-specific fashion identical to

other local anesthetics (542, 556), the hypothesis has developed that the apparent specificity of phenothiazines for antinausea and antipsychotic actions results from a particular drug distribution into various brain regions (542). The different distributions *in vivo* might arise because of slightly different physicochemical properties. For example, although both chlorpromazine and thiethylperazine can block nerve conduction, as well as protect erythrocytes from osmotic hemolysis, thiethyl perazine distributes preferentially into the vestibular nucleus (146a), this selective localization adequately accounting for the relatively specific antinausea action of this drug. Since chlorpromazine readily adsorbs or desorbs to various regions of the brain *in vitro* with equal affinity (349), the observed differences in chlorpromazine uptake by different brain regions *in vivo* must result from different permeability properties of the blood-brain barrier to chlorpromazine. The apparent specificity of some potent neuroleptics (pimozide, spiroperidol) on dopamine mechanisms may also be a result of selective drug localization in certain brain regions (19).

It is possible that the local permeability barrier for the drug near the sodium conductance channel may be different than the membrane permeability barrier for the drug to enter the tissue or the cytoplasm. It has been found, for example, that although the axoplasmic concentration of diphenylhydantoin attains 60 to 85% of the external concentration, there is no effect on nerve conduction unless all the surrounding axons are carefully removed or the axon treated with snake venom (phospholipases) to break down the permeability barriers near the excitable membrane (277, 332a, 507).

C. Selectivity arising from "cut-off" effects

As mentioned previously, anesthetic potency increases with lipid solubility. There is invariably a point at which further increase in lipid solubility, however, completely abolishes the anesthetic ability of the compound. This is known as the "cut-off" effect. Ferguson (199) and Ferguson and Pirie (200) explained this as being a consequence of the drug's low solubility in water such that insufficient quantities enter the animal to cause anesthesia. There is an optimum lipid solubility, therefore, for any particular set of anesthetic congeners (93), and Hansch and Glave (254) have studied this in considerable detail. The alkanes (pentane, hexane, octane *etc.*), for example, are all anesthetic (214); the cut-off occurs at decane which is not anesthetic (162, 425). The explanation for the cut-off with decane may be the solubility characteristics of the alkane hydrocarbons (208c, 390a–390c, 441a, 441b). The solubilities of the alkanes decrease until a minimum solubility is reached at about decane (208c, 390c), at which point a sharp discontinuity in solubility occurs (see fig. 12), the longer alkanes not now existing in true solution (molecular dispersion) but present as aggregates in suspension (390c). The aggregates may be extremely large, since many are filtered by a 0.45 micron-pored filter (390c). These aggregates may be difficult or impossible to absorb into the aqueous compartments of the body; they would essentially be treated as foreign bodies by the cell membranes of the alveolar cells lining the lung, which would phagocytose or pinocytose these aggregates;

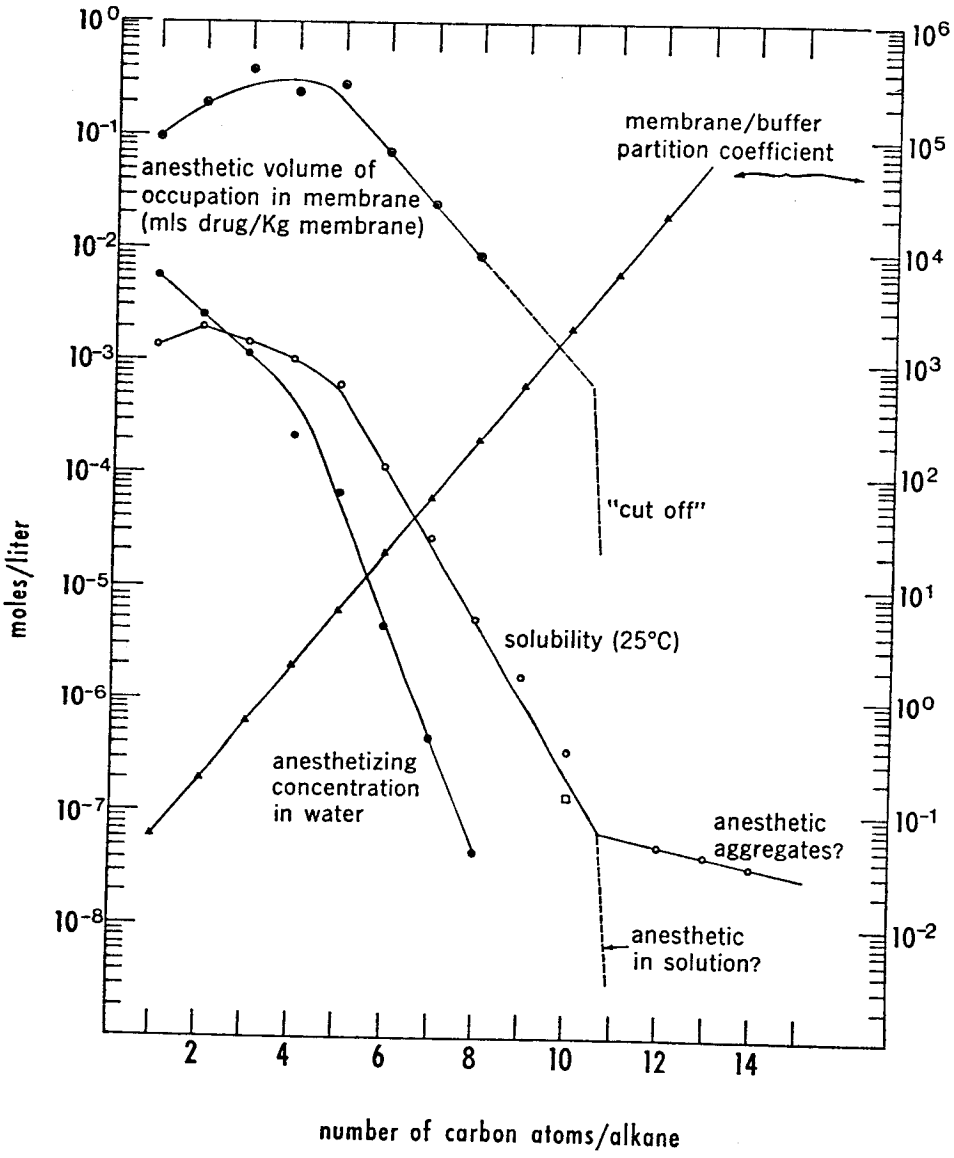

FIG. 12. The alkanes, decane and higher, are not anesthetic. This may result from the fact that these long alkanes are apparently not in true molecular solution but present as aggregates; square indicates solubility determination for decane from ref. 208c, circles are from ref. 390c. The membrane/buffer partition coefficients were determined from the octanol/water partition coefficients (364) and dividing by 5. The anesthetic concentration in the membrane phase is equal to the partition coefficient times the free anesthetic concentration in molecular solution in the aqueous phase. Since the free concentration is extremely low, the membrane concentration (as well as the membrane-occupying volume) will be low.

the aggregates could not diffuse readily into the space between Schwann cells and neurolemma; the aggregates would also tenaciously prevent single decane molecules from entering the water phase in molecular dispersion because of the strong total hydrophobic force of the aggregate for the monomer molecule. In effect, therefore, the cut-off for the alkanes may be explained by the aqueous phase as being the barrier to the anesthetic action of decane. As can be seen in figure 12, the membrane/buffer partition coefficients of decane, undecane, *etc.*, are very high. Despite these high coefficients, the membrane uptake of decane and undecane will be extremely low, since the partitioning only occurs between the molecules in free solution and the decane molecules in the membrane phase. Since the molecules in free solution must be extremely low (see fig. 12), the membrane concentration will also be low, regardless of the amount of time allowed for the animal to equilibrate with the decane *in vivo*.

These solubility discontinuities may also depend on the ionic strength, the calcium concentration and pH of the aqueous biophase surrounding the nerve cell membranes. For example, the long-chain fatty acids exhibit solubility discontinuities which are pH-sensitive (498b); this may explain why cut-off occurs for the antihemolytic fatty acids at around octanoic acid (511); this cut-off, however, may also depend on the Ca^{++} concentration in the medium (unpublished results).

The long-chain alkane alcohols do not exhibit any solubility discontinuities up to about pentadecanol (498b); it is interesting to note that antihemolytic effects are also obtained up to about pentadecanol, at which point cut-off occurs *in vitro*. *In vivo*, however, the alcohols beyond dodecanol are not anesthetic (80).

It is conceivable that there may be "local cut-off" effects within certain regions of the central nervous system. For example, the alcohol which diffused most quickly into the abdominal nerve cord was butanol; the higher alcohols diffused at lower or identical rates to butanol (180). More theoretical and experimental work must be done on such problems.

D. Selectivity arising from the negative charge of the anesthetic, such as with antiepileptics and barbiturates

It is known that negatively charged compounds (*e.g.*, diphenylhydantoin, ref. 4) are particularly effective in blocking the spontaneous firing of neurons made excitable by exposing them to a solution deficient in Ca^{++} and Mg^{++} (332a, 418a, 507, 621). Diphenylhydantoin, trimethadione and phenobarbital, for example, have this antispontaneous-firing effect at concentrations which are 20 to 100 times lower than the concentrations which block conduction of the artificially-electrically-evoked impulse (507). It is interesting that adenosine triphosphate (ATP) also has an antispontaneous-firing effect (341, 342, 453). The plasma-water or brain-water concentrations of diphenylhydantoin are of the order of 4×10^{-5} moles/liter which might be adequate to suppress spontaneous excitability of this nature (87, 203, 315, 640).

A possible membrane mechanism underlying this effect is that the negative drug crosslinks with both Ca^{++} (or Mg^{++}) and the membrane, thus causing

electrical stabilization. A general discussion of ATP-Ca^{++} complexes on the membrane is given by Abood (1), the principles of which may also apply to the membrane action of negative anesthetics. The situation appears to be rather complicated because the narcotic fatty acids (141, 524), as well as ATP, reduce the membrane-bound level of Ca^{++} (118, 547), while sodium pentobarbital has no apparent effect on membrane-bound Ca^{++} (547). Chronic treatment with diphenylhydantoin decreases excitability when subsequently tested *in vitro* (316); in addition to residual diphenylhydantoin remaining in the nerve, the drug may have altered (increased?) the membrane-bound Ca^{++}.

The differential effects of these negatively charged anesthetics on spontaneous firing (*i.e.*, local generation of impulses) and on standard impulse conduction affirms the idea that excitation-block and conduction-block are not the same phenomenon (286, 631, 633).

E. Selectivity arising from blockade of inhibitory cells

The well known excitation effects of anesthetics, including those caused by barbiturates (167) or fluorothyl (334, 335), may be caused by anesthetic blockade of inhibitory cells (109, 663).

F. Selectivity arising from differential inhibition of pre- and postsynaptic membranes

Differential effects of anesthetics on various regions within the CNS may result from different combinations of the following anesthetic effects on excitable membranes:

1) Suppression of spontaneous generation of an action potential in the axon membrane. The negatively charged anesthetics are particularly effective here, as already mentioned.

2) Suppression of conduction of an action potential along axons or modification of the conduction velocity of the action potential (614).

3) Suppression of invasion of the action potential into the presynaptic nerve terminals (82, 148, 379, 587, 588, 650). The work of Larrabee and Posternak (357) is often cited as evidence that "synapses" are more readily blocked than axons; the results may also be interpreted as evidence that the impulses did not invade the presynaptic terminals; a second difficulty is that some anesthetics (particularly the alcohols) sensitized or potentiated ganglionic transmission.

4) Differential suppression of excitability according to the axon diameter. It has long been observed that there was a tendency for small diameter fibers to be blocked more readily than wider ones (27, 147, 151, 152, 161, 183, 220, 237, 389, 436–438, 477, 515, 631–633). An example from the work of Uehara (631) is shown in figure 13, where the minimum blocking concentration of urethane is higher for wider fibers in frog sciatic nerve.

There are insufficient data on single neurons to conclude whether or not what Uehara has shown for urethane is true for other drugs. It is known that the concentrations required for general anesthesia are about $\frac{1}{20}$ the concentrations required for local anesthesia, and an example (taken from Carpenter, 104, 105)

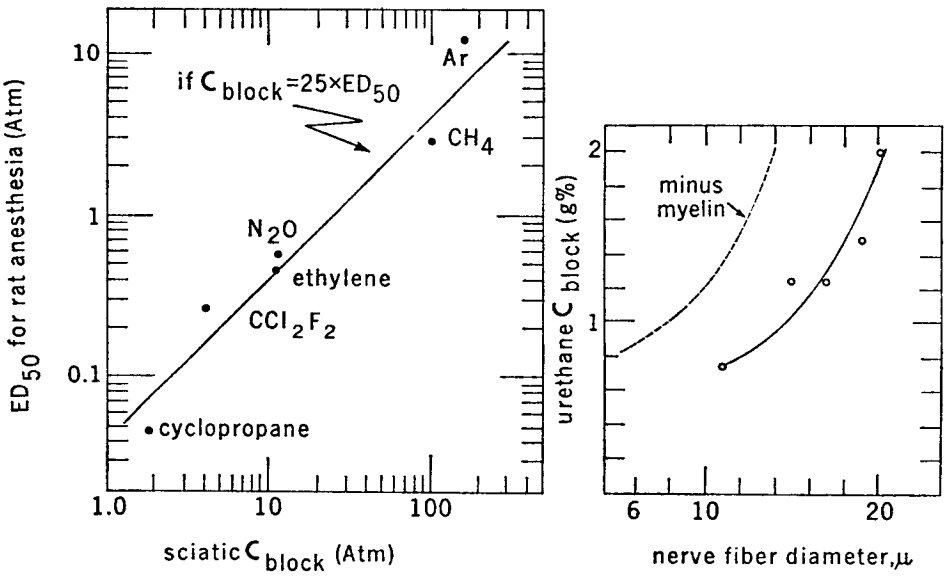

FIG. 13. The left side shows that the sciatic nerve-blocking concentrations for the gas anesthetics are about 25 times higher than those required for general anesthesia (adapted from ref. 104). The right side illustrates that the urethane concentration required to block conduction in single frog nerve fibers was directly proportional to the diameter of the fiber (adapted from ref. 631); the dashed line indicates the relation after allowing for the myelin thickness.

is shown in figure 13. If Uehara's results hold for other neutral anesthetics, general anesthesia and local anesthesia may be identical, except that in general anesthesia one is blocking certain neurons in the CNS which would be around ½ to 1 μ in diameter. Preliminary results in this laboratory, however, indicate that 15 to 20 μ-wide fibers (rabbit or frog sciatic neurons; see table 5) are blocked by chlorpromazine, methadone, barbiturates, morphine and benzyl alcohol at concentrations which are four times those which block 0.85-μ-wide fibers (rabbit vagus C fibers). The aliphatic alcohols (ethanol, propanol, pentanol *etc.*), on the other hand, block both 0.85-μ and 20-μ fibers at almost the same concentrations. Obviously much more experimental work needs to be done on this problem, wherein one tests the anesthetic susceptibility of a wide variety of neurons of a wide variety of species. If, however, no nerve fibers (including those down to less than 1 μ wide) are blocked by concentrations of ethanol lower than 0.5 M (see table 5), it will be necessary to conclude that general anesthesia with ethanol does not involve conduction blockade of any neurons within the central nervous system. Ethanol concentrations of 0.5 M are never attained in the plasma without killing the animal.

The low safety factor for impulse propagation in small diameter fibers may explain why anesthetics block the invasion of the action potential into the presynaptic terminals; it may explain why monosynaptic and polysynaptic reflexes are blocked (149, 153, 651) since either small nerve terminals or small inter-

neurons are involved; it may explain why sensory input to dorsal horn neurons is suppressed, since small cells in the substantial gelatinosa may be readily affected (15); it may explain why the halothane requirement is high in newborns and low in elderly people (238), on the basis that extensive ramifications of narrow neuron terminals develop in the first 3 years of life; and finally, it may explain why 0.5 M ethanol is required to block peripheral axons (see table 1), but only $\frac{1}{10}$ of this (0.04 M) to cause inebriation, general anesthesia and coma (168, 177, 178, 296).

5) Diminished neurosecretion from presynaptic terminals (650).

6) Enhanced neurosecretion from presynaptic terminals (488a).

7) Diminished re-uptake of neurotransmitter by presynaptic terminals.

Postsynaptic events:

8) Specific competition or antagonism of the neurotransmitter at the receptor site for the transmitter (42, 43, 176, 192, 263, 478, 507).

9) Non-specific (hydrophobic) distortion or dysconformation of the receptor site of the transmitter.

10) Threshold elevation and electrical stabilization of the postsynaptic membrane, associated with suppression of the sodium-carrying system (30, 67, 77, 109, 139, 148, 470, 567, 587, 588, 606).

11) Possible suppression of electrical cell-cell communication (34a).

G. Anesthetic selectivity arising because of hypothetical specific receptors for anesthetics (tetrodotoxin, steroids, progesterone, morphine, tetrahydrocannabinol)

There are specific receptors on the membrane for tetrodotoxin (13a–13e, 323, 431, 434); these are modified in the denervated membrane (13a, 13b; 256a, 493). Steroids and progesterone can act as anesthetics (134, 196, 244, 262, 460, 463, 557, 648), but it is not known whether these compounds have membrane receptors specific for anesthesia. Since these compounds are very lipid-soluble and surface-active (428a), since they suppress excitability of non-neural membranes (136, 645) and since they expand erythrocyte membranes (539), it appears probable that these anesthetic effects of steroids and progesterone are non-specific in the sense that the membrane concentrations of these compounds would be the same as those shown in table 5.

The membrane action of two narcotics, morphine and methadone, apparently fits the non-specific criteria (table 5). The analgetic potency of these compounds directly correlates with their lipophilicity (343), which indicates either a hydrophobic requirement to permeate tissue barriers, or a hydrophobic receptor site in the excitable membrane. In order to explain the fact that *levo*-rotatory opiate narcotics are of the order of 10 to 40 times more effective than *dextro*-rotatory ones, it is necessary to postulate that there are narcotic receptors in the membrane which are stereospecific. Although stereospecific binding has been detected for levorphanol (228), precise adsorption experiments in the author's laboratory have not revealed any stereospecific binding of *levo*-methadone over *dextro*-methadone in brain homogenate or brain regions or isolated synaptosomes.

It is interesting to note that the active ingredient of marijuana, Δ^1-tetrahydrocannabinol, also has antihemolytic effects (117) and presumably, therefore, can anesthetize nerve fibers. Some data for this compound are shown in table 5; the volume occupation in the membrane is low, 0.7%, but is of the right order of magnitude, considering the approximate experimental values for this compound.

H. Anesthetic selectivity arising from persistent binding in the nervous system

After a second injection of reserpine, there is no correlation between spontaneous motor activity and serotonin content in the brain (247, 384). Reserpine may have anesthetic-like action on cell membranes, on the basis that it has membrane-expanding action (556). Part of the explanation for the ability of reserpine to reduce spontaneous motor activity is that it may act as an anesthetic with persistent binding (444).

I. Anesthetic selectivity arising from stereospecific receptor sites in the membrane

One of the fundamental questions in the molecular pharmacology of the membrane action of anesthetics is to determine the biochemical nature of the membrane receptor site for these drugs. Since anesthetics act on pure lipid systems (140, 466, 466a) as well as pure protein systems, it is likely that anesthetics directly interact with both membrane lipid and protein rather than exclusively and directly affecting only one of these membrane components.

If experimental evidence for stereospecific binding or stereoselective action on membranes were available, it would suggest that the anesthetic directly attaches to membrane protein sites. Enantiomer differences in potency have been found with several anesthetics (99; see 512 and 609 for refs.), but on the whole the differences in anesthetic potency between optical antipodes of anesthetics are of the order of 1- to 5-fold (12, 13, 101, 279, 512, 646, 649). Åkerman *et al.* (11), for example, found that (+)-prilocaine was between 1.5- and 3-fold more potent than (−)-prilocaine in various tests for local anesthesia *in vivo*, but there was no difference *in vitro*. Part of the differences in enantiomer potency may be explained by unequal drug availability at the site of action; this results from differential rate of metabolism (11a) or unequal rate of absorption (11, 380a; see 512 for refs.). Åkerman *et al.* (12, 13) found that the enantiomers of N-(γ-diethylaminopropyl)-1,2,3,4-tetrahydronaphthalin-1-spirosuccinimide (or compound RAC 109) differ by up to about 5-fold in various tests for excitation-block potency, including isolated single nerve and muscle fibers.

The effects of enantiomers on various threshold phenomena seem to be stereoselective. For example, the RAC 109 enantiomers differ by 3-fold in elevating the threshold in single muscle fibers, but there is no potency difference in inhibiting the rate of rise of the action potential of the same cell. The binding of the RAC 109 enantiomers to membranes (erythrocyte ghosts or synaptosomes) is identical (512). The adsorption isotherms of *levo*-methadone and *dextro*-methadone to erythrocyte membranes as well as synaptosome membranes are also

identical to within 0.5% error (Seeman and Chau-Wong, unpublished). Stereospecific binding to albumin is less than 2-fold for the barbiturates (86) and is absent for the standard local anesthetics (626).

V. Membrane Expansion by Anesthetics

It has long been predicted that biomembranes should expand in the presence of anesthetics, on the basis that anesthetics penetrate and expand films spread at the air/water interface (124, 125, 536a, 537, 557–559, 563). It has now been found experimentally that anesthetics do indeed expand biological membranes, and this is the subject of this section.

There is an extensive literature on the anesthetic-induced expansion of films spread at the air/water interface. Some examples of this are the expansion of stearic acid monolayers by alcohols and local anesthetics (72, 566, 576, 577); the penetration and expansion of phospholipid and cholesterol monolayers by ethanol and local anesthetics (88, 221), by tranquilizers (146, 154), by steroids (221a) and by inert gases (48); and the expansion of lipoprotein films (extracted from lung) by gaseous anesthetics (124, 125) or of nerve-lipid films by alcohols and local anesthetics (578, 579).

Bulk phases such as hexane, olive oil or rubber also swell when gases or anesthetics become dissolved in these solvents or materials (359, 538). It is important to note that the swelling of these phases is approximately equal to the volume of anesthetic which enters the phase. (This is not true for biological membranes since biomembranes swell approximately 10-fold more than can be explained by the volume of anesthetic molecules in the membrane phase.) For example, from the data of Larsen *et al.* (359) chloroform causes approximately 0.2% swelling of a rubber membrane when the chloroform concentration within the rubber membrane is 0.05 moles per liter of rubber; the latter number corresponds to a van der Waals volume of about 0.21% (see table 5). The observed swelling of the rubber is roughly the same, therefore, as the anesthetic volume occupation in the membrane phase.

It is now known that biological membranes are also expanded by anesthetics. All the evidence for such biomembrane expansion comes from work on erythrocyte membranes. The validity of using these membranes to study the actions of anesthetics on excitable membranes has already been mentioned.

There are five types of erythrocyte experiments which indicate that anesthetics elicit membrane expansion:

1) *Anti-hemolysis.* This was first described in 1908 by Traube (622a), who found that amyl alcohol inhibited the hemolysis of erythrocytes in hypotonic solutions. Antihemolytic effects by various volatile anesthetics and urethane were described between 1913 and 1932, and these are summarized in references 303a and 539 to 542. The antihemolytic potencies for about 110 compounds are listed in tables 5 and 8 (see also refs. 113, 211, 249, 454, 525, 596).

It was Ponder (480) who first suggested that these antihemolytic effects could be explained by an increase in the critical hemolytic volume which might occur in the presence of "sublytic" concentrations of anesthetics.

TABLE 8

Molarities of neurotropic drugs which cause 50% antihemolysis (pH 7) (see also Table 5)

Hallucinogens		
LSD-25	(84*)	3×10^{-5}
Methysergide	(84*)	1×10^{-4}
Euphoriant		
Δ^1-Tetrahydrocannabinol	(117†)	8×10^{-6}
Steroids, anti-inflammatory drugs		
Pregnanolone	(539*)	1×10^{-5}
Epipregnanolone	(539*)	3×10^{-5}
Pregnandione	(539*)	4×10^{-5}
Progesterone	(539*)	7×10^{-5}
Etiocholanolone	(539*)	1×10^{-4}
Androsterone	(539*)	2×10^{-4}
Testosterone	(539*)	4×10^{-4}
Mefenamic acid	(318*)	8×10^{-5}
Flufenamic acid	(291*, 318*)	$8\text{–}20 \times 10^{-5}$
Indomethacin	(84‡)	1.5×10^{-4}
	(291*, 318*)	$3\text{–}10 \times 10^{-4}$
Phenylbutazone	(84‡, 415‡)	$1\text{–}5 \times 10^{-4}$
	(291*, 318*)	3×10^{-4}
Prednisolone tetrahydrophthalate	(3*)	1.4×10^{-3}
Cortisol hemisuccinate	(3*)	6×10^{-4}
Corticosterone	(3*)	2×10^{-4}
Dexamethasone	(3*)	4.3×10^{-4}
Oxyphenbutazone	(318*)	1.5×10^{-3}
Antiarrhythmic		
Procaine amide	(511*)	5×10^{-3}
Antipyretics, antirheumatics		
Sodium salicylate	(318*, 291*)	$2\text{–}4 \times 10^{-3}$
Acetylsalicylate	(318*, 291*)	$1\text{–}3 \times 10^{-3}$
Antihistamine		
Promethazine	(556*)	1.6×10^{-5}
Detergents		
Triton X-100	(541*)	1.1×10^{-5}
Na lauryl sulfate	(541*)	6×10^{-5}
Fat-soluble vitamin		
Vitamin A alcohol	(541*)	1×10^{-6}
Fatty acids		
Propionic acid*		5×10^{-3}
Butyric acid	(511*)	2.7×10^{-4}
Valeric acid	(511*)	5.8×10^{-3}
Hexanoic acid	(511*)	4.3×10^{-4}
Stearic acid	(541*)	8×10^{-6}
Adrenergic blocker		
Propranolol	(509*)	2.5×10^{-4}
Vasodilator		
Prenylamine	(239*, 405*)	1.5×10^{-5}
Antidepressant		
Imipramine	(155*)	$<1 \times 10^{-5}$
Tranquilizers		
Chlorpromazine	(350*)	1×10^{-5}
	(155‡)	1.9×10^{-5}

TABLE 8—*Continued*

Fluphenazine	(556*)	4 × 10^{-6}
	(155‡)	1 × 10^{-5}
Prochlorperazine	(556*)	1.6 × 10^{-6}
	(155‡)	6 × 10^{-6}
Butyrylperazine	(556*)	1 × 10^{-6}
Reserpine	(556*)	1.6 × 10^{-5}
Thioridazine	(556*)	5 × 10^{-7}
	(155‡)	5 × 10^{-6}
Trifluperazine	(556*)	1.2 × 10^{-6}
	(155‡)	6 × 10^{-6}
Haloperidol	(556*)	2.2 × 10^{-5}
Promazine	(155‡)	2.8 × 10^{-5}
Triflupromazine	(155‡)	1.1 × 10^{-5}
Perphenazine	(155‡)	1.5 × 10^{-5}

* Human erythrocytes.
† Rat erythrocytes.
‡ Dog erythrocytes.

2) *Critical hemolytic volume experiments.* Ponder's hypothesis was confirmed by Van Steveninck *et al.* (350, 596) who reported that 10^{-4} M chlorpromazine increased the V_c (critical hemolytic volume) by about 10%; Barac-Nieto *et al.* (40) found that triton X-100 increased the V_c. Seeman *et al.* (551) worked out the quantitative relation between the anesthetic-induced increase in V_c and the amount of membrane expansion in square microns; at 50% antihemolysis by any anesthetic, the membrane area of the intact erythrocyte expands by approximately 2 to 3%.

The anesthetics do not protect the erythrocytes from osmotic hemolysis by increasing the prelytic leakage of K^+ (510), which is normally about 10% of the intracellular amount (103, 494, 554). Very high concentrations of anesthetics, within 0.5 of the lytic concentration, do cause prelytic leakage.

The anesthetics do not protect the erythrocytes from osmotic hemolysis by slowing down the straining rate on the membrane (554), since it is known that cells hemolyse at the same V_c whether they undergo slow-hemolysis or rapid-hemolysis (375, 554).

The 2% to 3% expansion of membrane area (at 50% antihemolysis) is obtained by three different procedures wherein the V_c is measured: by Coulter counter methods on intact cells, by means of Van Allen hematocrit tubes or by micro-hematocrit capillaries (551). The maximum amount of membrane expansion which occurs at high concentrations of anesthetics is 5% to 7% (510, 551) at which point the membrane "buckles" inward or invaginates if the anesthetic is an amine (540, 544).

The anesthetic-induced expansion increases the surface area/volume ratio of the cell. According to the results of others (131; see refs. in 551), erythrocytes with higher area/volume ratios should be associated with a lower osmotic fragility. It would be interesting to know whether high atmospheric pressure (198) would prevent this anesthetic protection of erythrocytes.

3) *Membrane expansion of erythrocyte ghosts.* The addition of anesthetics to spherical erythrocyte ghosts (550) enlarges the spheres (see figs. 1B, 2B). The membrane expansion amounts to 1.5 to 3% increase in area at nerve-blocking concentrations (table 5). The entire population of different sized erythrocyte ghosts is expanded by the anesthetic (510); this holds for neutral, positively- and negatively-charged anesthetics.

4) *Membrane expansion of individual cells.* By direct measurement of the surface area of individual erythrocytes, Shrivastav and Burton (570) found that 0.004% Tween 80 expanded the membrane area by 14%.

5) *Anesthetic-induced changes in erythrocyte shape.* Qualitative evidence that anesthetics expand membranes comes from the shape-changes brought about by these compounds (248, 249, 350, 480, 551, 570). The negatively charged anesthetics tend to form crenated cell membranes (157), while the neutral or positively charged anesthetics tend to form cup-shaped (157, 350, 540) or "dog-bone-shaped" cells (570).

Some of the anesthetics, such as chlorpromazine, also reduce erythrocyte sickling (257, 373, 391); to be clinically effective, however, it requires very large doses of chlorpromazine in order to maintain high membrane-expanding concentrations in the aqueous and membrane phases (458, 492).

Qualitative findings suggesting membrane expansion have also been found by electronmicroscopy where it has been observed that chlorpromazine (540) or primaquine (223) cause membrane invagination without requiring any ATP (*cf.* 473).

A. Comparison between membrane expansion, and the membrane-occupying volume of the anesthetic

In trying to understand the events in anesthetic-induced membrane expansion, the simplest mechanism to be considered first is that of an increase in the volume of the membrane as a result of the "burying" of the anesthetic molecules right into the membrane (423–425).

It turns out that the amount of membrane-volume expansion or membrane-area expansion is of the order of 10 times the bulk volume of the anesthetic molecules which are absorbed in the membrane phase. The membrane-area expansion is of the order of 2 to 3% under conditions of local anesthesia (see previous section); a 2% expansion of membrane area is associated with a 3.5% swelling of the membrane volume, assuming uniform swelling in all directions. The anesthetic volume occupying the membrane phase, however, is only about 0.3% (see table 5); in fact, this latter value is probably closer to about 0.25% if the anesthetic volume is expressed as cm^3 per kg of hydrated membrane, rather than dry membrane. (The membrane is about 30% hydrated; see refs. in 346.)

Under conditions of general anesthesia, membrane expansion is also about 10 times greater than the bulk volume of the anesthetic molecules in the membrane. For example, it has been found that surgical concentrations of halothane, chloroform, ether and methoxyflurane expand human erythrocyte membranes by around 0.4% in area (552) (which is equivalent to about 0.6% increase in membrane volume).

Pressure reversal of anesthesia. It is also known that high atmospheric pressure antagonizes or reverses general anesthesia (186, 250, 310–313, 367, 409) as well as local anesthesia (594). Lever *et al.* (367) have calculated that the pressure which reverses general anesthesia is associated with a compression of about 0.4%, a value identical to that found for the anesthetic-induced expansion of the erythrocyte membrane under conditions of general anesthesia. The volume of anesthetic which occupies the membrane under conditions of general anesthesia, however, is not 0.4%, but around 0.02% or less (see tables 6 and 7). Johnson *et al.* (313a) have evidence indicating that pressure reversal of anesthesia (caused by ethanol, ether, butanol, pentobarbital or chloroform) is not explained by a squeezing out of molecules from the membranes.

It may be concluded, therefore, that the presence of an anesthetic molecule within the membrane phase expands the membrane by approximately 10 times more than its van der Waals volume. (This is very different from the case of anesthetic-induced swelling of rubber (359) or the swelling of olive oil and hexane by gases (538), where the amount of swelling is essentially accounted for by the volume of molecules dissolved therein.)

B. Molecular mechanisms of membrane expansion by anesthetics

Anesthetics might expand biological membranes by combinations of the following possible mechanisms:

1) *The anesthetic occupies space within the membrane phase.* As just discussed, the volume-space occupation cannot account for more than 10% of the observed membrane expansion.

2) *Disordering and expansion of lipid regions of membrane.* (See section VI.)

3) *Membrane expansion by anesthetic-induced ice formation in the membrane.* Pauling (471) and Miller (411) have suggested that anesthetics induce ice formation within or adjacent to the membrane phase. No direct test of this hypothesis has yet been made, but Seeman *et al.* (555) have found that the erythrocyte permeability to water (the hydraulic permeability coefficient, L_p) is increased by anesthetics. Since it is thought that L_p reflects the amount of membrane hydration, membrane expansion may result from a small increase in membrane water. High atmospheric pressure may reverse this by dehydration or decomposing the ice (589).

4) *Anesthetic-induced conformation changes in membrane proteins.* Since anesthetics are known to produce conformation changes in proteins (35), it is possible that the membrane expands as a result of distortion or expansion of the membrane proteins. High pressure reversal may be associated here with an altered state of membrane protein-protein interactions (22).

5) *Anesthetic-induced alteration in membrane-Ca^{++}.* The anesthetic might displace some membrane-associated component which normally keeps the membrane in a condensed state. It is known that Ca^{++} condenses lipid monolayers spread on a Langmuir trough (see 258 for refs.). It is also known that when Ca^{++} adsorbs to the cytoplasmic aspect of the membrane, the membrane becomes rigid and difficult to deform (652). Chlorpromazine displaces membrane-bound Ca^{++} (see fig. 2D) and could, therefore, readily expand the membrane in this

way (347). Neutral anesthetics, on the other hand, increase the membrane-bound Ca^{++} (see fig. 1D; 118) even though they, too, expand the cell membrane. In general, chlorpromazine produces a greater amount of membrane expansion than do the alcohols; this might be explained by the fact that the alcohols do not displace membrane-bound Ca^{++}, but the anesthetic amines do.

6) *Aasorption-extension hypothesis of Schneider.* Anesthetics might adsorb to the membrane, altering the amount of water in contact with either side of the membrane, and consequently altering the interfacial tension at the membrane-water interface. The net result of these effects would be for the membrane to undergo extension (see ref. 532).

7) *Anesthetic inhibition of contractile enzymes or proteins in the membrane.* One of the mechanisms of anesthetic-induced membrane expansion might be that the anesthetic inhibits a contractile membrane-associated ATPase. The evidence for such proteins is still not clearly established (75, 465, 661). It has been shown by Landmark and Øye (353) that the phenothiazine local anesthetics have membrane-expanding actions at concentrations which only very slightly inhibit the membrane's $(Na^+\text{-}K^+)$-ATPase.

If membrane narcosis results from a membrane expansion, and if an elevation in temperature elicits membrane expansion (375, 545), then why does not a rise in temperature by itself induce narcosis? The answer may be that the anesthetic induces and apparently primarily expands the hydrophobic regions of the membrane, whereas heating the membrane merely causes increased disorder and expansion of all membrane components.

VI. Membrane Fluidization and Membrane Disordering by Anesthetics

Anesthetics cause a "loosening" of the components of the membrane. This may be referred to as a fluidization or disordering of the membrane (396–398). The membrane-fluidizing effects of anesthetics fall into the following categories:

A. Increase in anesthetic mobility within the membrane

The mobility of anesthetic molecules within the membrane can be monitored by nuclear magnetic resonance relaxation (396–398). At low concentrations the anesthetic is strongly immobilized by the membrane structure. For example, the rotational relaxation rate of benzyl alcohol in free solution in the absence of membranes is 1.73 sec^{-1}; the value for benzyl alcohol relaxing within the membrane is 570 sec^{-1}, indicating a restriction of molecular motion of the anesthetic in the membrane (398). [The relaxation rate of benzyl alcohol dissolved in corn oil is 8.9 sec^{-1} (ref. 398).]

At anesthetizing concentrations of benzyl alcohol, the mobility of the anesthetic in the membrane increases to a maximum value of 189 sec^{-1} for the relaxation rate. Examples of this effect for the aliphatic alcohols are illustrated in figure 1C. It can be seen in this figure that at the sublytic or lytic concentrations of the anesthetics the mobility of the anesthetic molecule once more becomes restricted. This latter effect may be adequately explained by evidence which

indicates that anesthetic-binding sites in the membrane protein are unmasked at lytic concentrations of anesthetic (398).

These mobility effects occur in a variety of biological membranes, including erythrocyte ghosts, synaptosomes, myelin and vagus nerve membranes; both neutral and charged anesthetics are effective (397).

B. Altered membrane rheology in the presence of anesthetics

Very little work has been done on the rheological characteristics of the membrane in the presence of anesthetics. There is suggestive evidence that chlorpromazine increases membrane deformability (76), and that cyclopropane concentrations higher than 20 mg per 100 ml (5 mM) increase the yield stress of human erythrocytes (26); this latter effect may be related to a fluidization of the membrane. There is need for a systematic study of anesthetic action on membrane deformability by the techniques described by Weed *et al.* (652).

C. Anesthetic-induced changes in the state of the membrane, as monitored by fluorescent hydrophobic probes

The properties of fluorochromes, such as 8-anilino-1-naphthalene sulphonic acid (ANS) are such that they are sensitive to the hydrophobic nature of their microenvironment. When they bind to the membrane, measurement of quantum yield and wavelength of maximum fluorescent emission give information on the hydrophobic nature of their binding site; measurement of excited-life-times and polarization gives information on membrane fluidity; and energy-transfer-quenching given information on the protein-probe interaction. They are currently being used to monitor alterations in membrane substructure caused by anesthetics (195, 590a, 590b). A sample of the type of result with this technique is shown in figure 1C, where low concentrations of the alcohol anesthetics produce a decrease in ANS fluorescence, and high concentrations enhance the fluorescence (509a, 590c). These effects are interpreted by Spero as a membrane structure change in the number of available sites for ANS, and probably reflect conformation changes in membrane protein.

Modification of energy transfer between membrane protein tyrosine and tryptophane groups by anesthetics supports this view (509a). In addition, comparison of the effects of different anesthetic families, on a number of different fluorescent parameters, suggests that their binding sites are not identical, and neither is the extent of the hydrophobic membrane perturbation they induce (509b).

D. Anesthetic-induced fluidization of biomembranes, as monitored by electron spin resonance techniques

The mobility of nitroxide-containing compounds within the membrane can be monitored by electron spin resonance methods, and the membrane effects of anesthetics using this approach have been reviewed (396). Hubbell *et al.* (279a–279c) have found that anesthetics cause a melting or disordering of the membrane such that more hydrophobic molecules enter into the membrane's hydro-

phobic regions; the spectra of the nitroxide molecules within the membrane phase indicate that the anesthetics increase the molecular freedom of motion in the membrane. Trudell *et al.* (624a) found that halothane and methoxyflurane decreased the ordering of lipid within the bilayer structures; increased atmospheric pressure (in the presence of anesthetics) restored the ordering of the molecules.

The sulfhydryl groups of the membrane (tagged with a spin-labeled iodoacetamide), on the other hand, appear to become less mobile and more inaccessible in the presence of anesthetics (275).

E. Effects of tranquilizers and anesthetics on the viscosity and fluidity of lipid monolayers and membranes

The phenothiazine tranquilizers increase the surface viscosity of lecithin and cholesterol monolayers at the air/water interface in the absence of Ca^{++} (537). This increase, however, is much smaller than that caused by the addition of Ca^{++} to the lecithin monolayers (537). Because tranquilizers readily displace membrane-bound Ca^{++} (347), these drugs would be expected to reduce the surface viscosity of lipid films if studied in the presence of Ca^{++}.

Johnson and Bangham (312) found that butanol, chloroform and ether (all at concentrations which cause local anesthesia) increased the entropy, ΔS, of liposomes by approximately 2 calories per degree, evidence compatible with the general view that anesthetics disorder membrane lipids.

More direct evidence for lipid disordering comes from ESR studies on the effect of alcohols on oriented lipid multibilayers, wherein erythrocyte and brain lipids contain a small amount of added spin-labeled cholestane (469). An example of this from the work of Paterson *et al.* (469) is shown in figure 1F, where the per cent change in B/C of the ESR spectrum of the spin-labeled cholestane is shown; B and C are the amplitudes of the two hyperfine splittings of the spectrum and which are separated by 7 gauss. A depression in B/C indicates that the cholestane became tilted away from the normal position perpendicular to the multibilayers. In addition to those alcohols shown in figure 1F, thymol, benzyl alcohol, promethazine and chlorpromazine had the same type of effects (469). Cuthbert (140) has reviewed the actions of drugs on membrane lipids.

F. Ultrastructural evidence for membrane fluidization by anesthetics

The author's current work, with freeze-fracture electronmicroscopy (547a), indicates that higher concentrations of the amine anesthetics, including the phenothiazine tranquilizers, rearranges the membrane globules (each about 80 Å in diameter) into groups, leaving large globule-free zones of membrane which invaginate.

G. Anesthetic-induced changes in the fluidity of membrane water

It has been suggested that anesthetics induce ice, clathrates (171), or mixed-clathrate (133) formation of the membrane-associated water (107, 120, 121, 173, 411, 412, 471) in cooperation with protein side-chains (307). There is vir-

tually no direct experimental evidence (197) to support this interesting idea. The little evidence that does exist suggests that the anesthetics "melt" or fluidize the membrane-associated water. For example, Seeman *et al.* (555) found that neutral or charged anesthetics increased the hydraulic flow of water molecules through the erythrocyte membrane. Schoenborn *et al.* (534), on the other hand, calculated that xenon increased by 15% the irrotationally bound water associated with hemoglobin. It has been found that procaine increases the proton magnetic resonance (PMR) line-width of the water protons (212). Although this broadening in line-width is compatible with an increase in water viscosity, it is impossible to decide whether this has anything to do with the state of membrane-associated water since only a small fraction of the cell's organized water (114, 132, 213) can be associated with the membrane (less than 1%). The study of anesthetics on the water fluxes across tissues also provides inadequate information (50, 51, 642), because water movement primarily occurs between cells, and secondly, the anesthetics reduce the spontaneous motion of cells and thus reduce the mixing efficiency around the cells. Experiments involving temperature variations (569) in the presence of anesthetics are also virtually impossible to interpret since the baseline properties of the membrane also vary with temperature in the absence of anesthetics (115, 116, 243, 271, 375, 383, 500, 594).

In order to settle this question, it will be necessary to add anesthetics to a highly concentrated suspension of membranes having 70% membrane solids, the rest being water all of which would be associated with the membrane; PMR studies under these conditions should prove fruitful. It may then not be necessary to use D_2O which antagonizes the anesthetic potency to varying extents (380).

VII. Anesthetic Actions on Membrane Proteins and Enzymes

. . . the way in which anesthetics act on the nerves . . . consists in a semi-coagulation . . . of the nerve cells, a coagulation which would not be permanent, the anatomical unit being able to return to its normal state after the toxic agent is eliminated.

Claude Bernard,
Leçons sur les anesthésiques et sur l'asphyxie, 1875 (see ref. 363)

Claude Bernard's idea of "reversible coagulation" is in modern terminology referred to as reversible conformation change in proteins. It is still not clear whether the anesthetic actions on membrane-associated enzymes are actually necessary for the inhibition of the nerve impulse, since Mueller and Rudin (421) have found that local anesthetics will block action potentials of lipid bilayers to which only non-enzymatic protein has been added. Nevertheless, there can be no doubt that the overall, non-electrical responses of the cell or the tissue very much depend on what the anesthetic does to enzyme systems, such as the arrest of mitosis by anesthetics (14, 15, 85, 445). The anesthetic action on enzyme systems has been pioneered and reviewed by Quastel (489).

Although there are a number of studies describing the binding or adsorption of anesthetics and tranquilizers to pure proteins (108, 188, 189, 305, 388, 533, 664), there is very little information available on the adsorption of anesthetics

TABLE 9

Stimulation and/or inhibition of membrane-associated and soluble enzymes by anesthetics and tranquilizers

	Stimulation	Inhibition
Na^+-K^+-ATPase	Deoxycholate (314) Dodecyl sulfate (314) Lubrol (314) Pentobarbital (359) Dibucaine (20) Tetracaine (20) N_2 (623) Triton X 100 (78) Diphenylhydantoin (60, 201, 227)	Promazine (144, 353) Thioridazine (144, 353) Chlorpromazine (9, 10, 28, 122, 144, 501) Imipramine (28, 122, 144) Desipramine (28) Procaine (20) Dibucaine (20) Tetracaine (20) Haloperidol (630) Barbiturates (122, 359) Diazepam (630) Diethylether (629) Halothane (629, 359) Alcohols (297, 298, 317, 625) Kr (232) Xe (232) N_2O (232, 233) Fatty acids (141) Cyclopropane (623)
Mg^{++}-ATPase	Alcohols (612, 613) Ether (202)	Amytal (662) Promethazine (662)
Mitochondrial ATPase	Phenols (600)	Halothane (583) Phenols (601)
Cholinesterase	High surface pressure (580)	N_2O, Xe, SF_6, Kr (535)
Adenyl cyclase	Alcohols (231) Dodecyl sulfate (474) Chlorpromazine (666) Thymol (666) Triton X-100 (474)	Propranolol (506, 568) Phenothiazines (634a)
Adenylate kinase	Chlorpromazine (501)	
Luciferase		N_2O (251) Diethyl ether (251, 627, 654) Halothane (251, 627, 654) Cyclopropane (654) Chloroform (251, 654)
Oxygen consumption		Miscellaneous (355, 358)
NADH-CoQ reductase		Halothane (256)
Tryptophan oxygenase		Chlorpromazine (426)
D-Amino acid oxidase		Phenothiazines (406)
Lipoamide dehydrogenase		Phenothiazine sulfoxides (406)
Phosphotransferases, phosphohydrolases, pyrophosphatases	Triton X-100, cetrimide deoxycholate, tweens, Na lauryl sulfate (584)	
Cytochrome oxidase		Ethylcarbamate (326)
Formamidase	Alcohols (536)	
Invertase		Propane (381)
Cytochrome C autoxidation	Alcohols (322)	
Aniline hydroxylase	Halothane (635) Methoxyflurane (635) Trichlorethane (635)	

to proteins isolated from membranes. Metcalfe *et al.* (398) found that such proteins, extracted from erythrocyte membranes, had a much higher partition coefficient for benzyl alcohol than the native membrane; this suggested that many of the anesthetic binding sites of the membrane protein were masked when the protein was in its normal location in the membrane. The partition coefficient of an anesthetic in soluble proteins is generally less than that in the membrane (*e.g.*, 345).

There is practically no information on the conformation changes which anesthetics induce in isolated membrane proteins (but see 398), although there are excellent studies available on such changes (*alpha* and *beta* helix content, H^+-equilibrium, ultraviolet absorption *etc.*) in pure proteins and polypeptides (35, 59, 290, 308, 351, 653, 665).

The anesthetic-induced expansion of the membrane is 10 times the anesthetic volume of occupation in the membrane. The membrane event which could most readily account for this would be a conformation change in the membrane proteins and enzymes. Eyring's rate theory (see 186 for refs.) predicts that the rate of a reaction is associated with a volume change upon activation (ΔV); if ΔV is large then the rate of the reaction would be sensitive to atmospheric pressure. Penniston (472) has found that high atmospheric pressure causes conformation changes and stimulates enzymes which are protein monomers (*e.g.*, trypsin, peroxidase *etc.*); multimeric enzymes, such as the membrane ATPases, are inhibited by pressure, and Penniston explains this as not resulting from conformation changes but from dissociation of the protein-protein non-covalent interactions. Physical compression of a monolayer (*i.e.*, high surface pressure) of cholinesterase at the air/water interface stimulates the enzyme (580).

Since pressure antagonizes the membrane action of anesthetics, and since pressure can inhibit or stimulate enzymes (472), it is not surprising that anesthetics can also either inhibit or stimulate membrane-associated or soluble enzymes (see table 9). The activation of some of the membrane enzymes may result from the membranes (usually in a closed vesicular shape) becoming more permeable to the substrate (78, 314).

The membrane Na^+-K^+-ATPase normally is not electrogenic in nerve cells, although it can become electrogenic immediately after a tetanic train of stimuli (611a). Complete inhibition of this enzyme by ouabain in peripheral nerve fibers has no effect on the electrical properties or excitability of the nerve cell. It appears unlikely that this enzyme is involved in the basic mechanism of anesthetic blockade, since direct application of ouabain to nerve-tissue invariably produces convulsions (52, 370). Another reason is that the membrane-expanding (and nerve-blocking) concentrations of the phenothiazine tranquilizers occur at levels which only inhibit the Na^+-K^+ ATPase by about 1 to 5% (353). High, anesthetizing pressures of N_2, in fact, stimulate the Na^+-K^+ ATPase (318a).

VIII. Anesthetic Actions on Membrane Calcium

Ca^{++} serves at least four roles in membrane function: 1) It is required for electrical stability of the cell membrane (see refs. in 430); 2) Ca^{++} influx partly con-

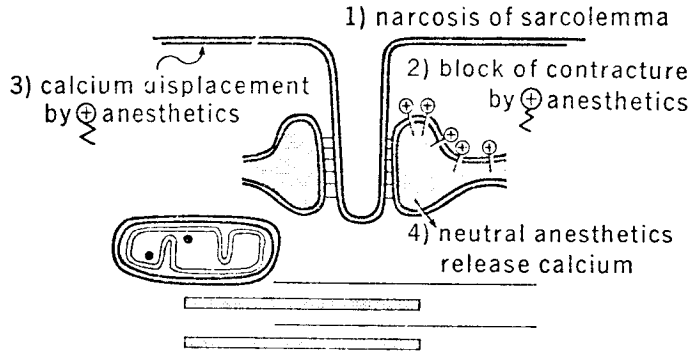

FIG. 14. A diagrammatic summary of the various actions of anesthetics on muscle membranes. 1) the sarcolemma excitability is blocked; 2) the cationic anesthetics adsorb to the reticulum membrane, preventing release of Ca^{++} and thus stopping muscle contracture; 3) the cationic anesthetics displace sarcolemma-bound Ca^{++}, blocking stimulus-response coupling; 4) the neutral anesthetics (*e.g.*, halothane, alcohols, or uncharged form of anesthetic amines) increase the release of Ca^{++} from reticulum, thus tending to promote contracture.

tributes to the inward current of the action potential (34, 430); 3) Ca^{++} is needed to couple the electrical events of the membrane to the physiological response of the cell (55, 56, 165); 4) intracellular Ca^{++} may regulate the permeability of the cell membrane for both ions (655) and neutral solutes (274). Anesthetics interfere with all these events, as summarized in figure 14.

A. Displacement of membrane-bound Ca^{++} by the anesthetic amines

The local anesthetic amines (procaine, chlorpromazine, tetracaine, quinidine) readily adsorb to biomembranes and compete with and displace the membrane-bound Ca^{++} from the fixed negative sites of the membrane (70, 193, 347); one membrane-bound calcium ion competes with two amine molecules (347). An example of this displacement is shown in figure 2D.

Although the majority of the membrane-bound Ca^{++} is associated with membrane protein (206), there are no studies describing the interaction of anesthetics with membrane-protein-bound Ca^{++}. There is considerable work demonstrating that anesthetics displace the Ca^{++} adsorbed to phospholipids; this occurs with propranolol (440), all narcotic amines (422), procaine-type anesthetics (63, 66, 190, 191, 258, 448). The anionic anesthetics (barbiturates, fatty acids), on the other hand, increase the binding of Ca^{++} to phospholipids, as would be expected from a fixed charge point of view (63, 66). These competitive phenomena may be the basis for the competition between Ca^{++} and procaine on the excitable membrane (65).

B. Inhibition of stimulus-response coupling by amine anesthetics

Since Ca^{++} is required for excitation-contraction coupling (55, 56) and stimulus-secretion coupling (165), and since the amine anesthetics displace plasmalemma Ca^{++}, this may partly explain the inhibitory effect of local anesthetics, propranolol and chlorpromazine on adrenomedullary secretion (303, 513, 514), and the inhibition of the contractile force of muscle (354).

C. Membrane-bound Ca^{++} is increased by neutral anesthetics which sensitize nerve or muscle

There are four types of "sensitizing effects" which anesthetics elicit by their membrane actions:

1) Low concentrations of various alcohols and volatile anesthetics can sensitize or potentiate contractions of muscle to drug or electrical stimulation (184, 302, 321, 441, 487, 491, 518–521, 591, 622).

2) Alcohols, phenols, acetone and other volatile anesthetics increase the frequency of miniature end-plate potentials.

3) The volatile anesthetics sensitize mechanical stretch receptors and afferent nerve endings (464, 656, 657).

4) Neutral anesthetics, including both the volatile compounds and the local anesthetics in their neutral form, can produce muscle contracture, particularly in the presence of caffeine (55–58, 193, 320, 599).

The first three sensitizing effects may be partly explained by the fact that many neutral anesthetics increase the binding of Ca^{++} to the cell membrane (175, 547); this occurs with alcohols (175, 547), ether, chloroform, acetone and benzyl alcohol, and examples of the effects of alcohols are shown in figure 1D. The membrane-bound Ca^{++} is very sensitive to acetone and to the lower alcohols, rising by 6% at 0.09 g% ethanol (20 mM) which is the intoxicating plasma concentration of ethanol.

It is not yet known whether the anesthetic-induced increase in membrane-bound Ca^{++} is an increase in the binding to membrane protein or the membrane lipid. Seeman *et al.* (547) have found that ethanol increases the membrane affinity for Ca^{++}, rather than increasing the number of binding sites. This increased affinity can be explained by a conformation change in membrane protein, but can also be explained by an altered spacing of the negative sites of phospholipids toward the optimum spacing of 9.6 Å for binding the hydrated calcium ion (258). Thyrum *et al.* (617) have found, for example, that these sensitizing neutral anesthetics can increase the binding of Ca^{++} to interfacial phospholipid films.

D. Effects of anesthetics on Ca^{++} fluxes across plasma membranes

There are not many studies of the effects of anesthetics on Ca^{++} fluxes across cell membranes. The major difficulty is to be able to distinguish between the effect of the anesthetic on the fluxes into (or from) the membrane-bound pool of Ca^{++}, and the transmembrane fluxes of Ca^{++} into (or from) the cytoplasm (138, 319). The concentration of Ca^{++} in the membrane phase is generally about 10 to 20

times higher than that in the cytoplasm (118), and this fact must be considered in interpreting the findings. For example, procaine and tetracaine increase the release-rate of $^{45}Ca^{++}$ from nerve and muscle (280, 340) presumably by displacing the radioactive calcium ions bound to the membranes (347). The transmembrane fluxes of Ca^{++}, however, are invariably inhibited by the positive anesthetics (55, 56, 165, 194, 303, 513, 514). Neutral anesthetics generally increase membrane permeability to all ions, including Ca^{++} (202, 447, 599, 616).

E. Effects of anesthetics on Ca^{++} fluxes across reticulum membranes

The general observations here are that positively charged anesthetics adsorb to the reticulum membrane vesicles (37), presumably form a layer of positive charges around the vesicle (38, 616), displace the loosely adsorbed Ca^{++} (616), and, most important, block the transmembrane influx or efflux of Ca^{++} across the vesicle (106, 447, 616, 659). This mechanism appears to be the basis for Feinstein's important observation that contracture of muscle elicited by caffeine can be blocked by the anesthetic amines (189a). The neutral anesthetics, including the neutral form of the anesthetic amines (which exists at high pH), make the reticulum membrane more permeable to Ca^{++}, and, by releasing the Ca^{++} sequestered within the reticulum space, can cause the muscle to go into contracture (202, 320, 447, 599, 616). These contractures associated with release of Ca^{++} from the reticulum can be overcome by the administration of a charged anesthetic, such as procainamide (599), and this fact may be of life-saving significance in treating the contracture of malignant hyperthermia (see refs. in 599).

F. Effects of anesthetics and tranquilizers on the Ca^{++} fluxes across mitochondrial membranes

The positive anesthetics generally reduce the entry of Ca^{++} across mitochondrial membranes (309, 620). There is an observation that the positive anesthetic butacaine actually increases the entry of Ca^{++} into the mitochondria in the first few seconds after the addition of the drug (394, 395); this is probably merely a transient increase in the amount of Ca^{++} within the mitochondria as a result of butacaine passively displacing Ca^{++} which is adsorbed to the internal side of the inner membrane of the mitochondrion. In an important paper, Godfraind *et al.* (226) report that iontophoretic application of metabolic inhibitors (dinitrophenol, oligomycin, iodoacetate, *etc.*) hyperpolarized the cell membrane (by opening the K^+ channel), thereby blocking spontaneous firing and discharges evoked by acetylcholine; Krnjević and his colleagues (226) thus propose that general anesthetics may do the same thing as dinitrophenol; the anesthetics inhibit mitochondrial activity, and release Ca^{++} which in turn hyperpolarizes the nerve cell membrane.

IX. Anesthetic Actions on Membrane Flow in Neurosecretion and Granule Secretion

This section reviews the anesthetic effects on secretion of membrane-bound materials in both the nervous system and in non-neural tissues, the mechanisms being rather similar.

A. Anesthetic effects on neurosecretion

Quastel *et al.* (244a, 488) has found that all types of anesthetics increase the frequency of miniature end-plate potentials (MEPPs) at the neuromuscular junction. Anesthetics which increase the frequency of MEPPs or increase the end-plate potential or facilitate nerve-muscle transmission include alcohols (217, 450–452, 559), acetone (451), barbiturates (652a), phenols (62, 219, 338, 416, 459) and procaine (244a, 619). Quastel *et al.* (488) have also found that the anesthetic-induced increase in the final release step in neurosecretion does not require any extracellular Ca^{++}.

The most likely explanation for enhanced neurosecretion by the anesthetics is the membrane fluidization caused by these drugs. The increased fluidity of both the cell membrane (plasmalemma) and the membranes of the secretion granules (or vesicles) may lead the two sets of membranes to fuse, in a manner analogous to virus- or lysolecithin-induced fusion of cells.

Enhanced neurosecretion or facilitation by anesthetics has also been found in the superior cervical ganglion with ethanol (357), chlorpromazine (182) or ether (356).

The increased release of dopamine in the central nervous system by chlorpromazine (19, 119, 484) or reserpine (33, 605) such that extrapyramidal disorders develop (327) is presumably the same type of phenomenon that occurs at the neuromuscular junction or in the ganglion. The increased release of dopamine granules causes a derepression of granule synthesis and new dopaminergic granules are synthesized (484).

Anesthetic-stimulated neurosecretion can, therefore, lead either to excitatory or depressant effects (490), depending on the distribution of the anesthetic and depending on which neurosecretory cells are most affected. Phenol markedly increases the monosynaptic response in the cat spinal cord (39). This synaptic facilitation was found at both excitatory and inhibitory synapses, and is consistent with the hypothesis that convulsant phenols act by increasing the amount of transmitter released (39).

While anesthetics may stimulate neurosecretion, the overall effect of these compounds on the junctional or synaptic transmission is depression in many cases (218, 224, 324, 325, 602, 634, 636, 650). Presumably under these conditions the presynaptic depression of the action potential, as well as the postsynaptic depression of excitability, dominate the situation, masking the enhanced neurosecretion. There may be a clinical analogy to this in the case where low dosage of fluphenazine (up to 25 mg/day) produces extrapyramidal symptoms (presumably *via* dopamine depletion), while high doses (100 to 1200 mg/day) do not produce extrapyramidal symptoms (495).

B. Anesthetic effects on granule secretion in non-neural tissues

Mast cells. Careful electronmicroscopic analysis indicates that the degranulation of mast cells starts by a fusion of the granule membrane with that of the cell membrane (502); other granules then fuse in sequence until the cell is filled by a system of complicated cavities, all of which communicate directly with the extracellular space, but which still contain the osmiophilic cores of the granules (502).

This mechanism is similar to that which occurs in exocrine tissues (see refs. in 502), and is seen with $^{48}/_{80}$ (502), ATP (602a), chlorpromazine (306), and probably also with reserpine (222) but detailed ultrastructure on this last drug is not available. It is important to point out that if high concentrations of chlorpromazine are used (10^{-4}–10^{-3} M), all the membranes are disrupted by this surface-active drug (306).

Adrenergic cells. A variety of anesthetics elicit exocytosis of the catecholamine-containing granules; this includes ethanol (475, 476), cyclopropane (441c, 486a), chlorpromazine (385, 488, 637–639), reserpine (17, 69, 181, 272) and tetracaine (644a). The positively charged anesthetics, however, may also cause reduced granule secretion by reducing the influx of Ca^{++} (166); the final effect, therefore, on any particular tissue will depend on whether the membrane-fluidizing effect dominates or whether the inhibition of Ca^{++}-influx dominates (see 81). The muscle membrane hyperpolarization caused by cyclopropane appears to be a result of catecholamine release (326a).

Platelets. Phenothiazines, reserpine and local anesthetics release 5-hydroxytryptamine (6, 387, 462, 485, 486, 610) presumably by causing membrane-membrane fusion.

Phagocytosis. Chlorpromazine, imipramine, and morphine reduce phagocytosis (344, 671).

X. Anesthetic Effects on Solute Translocation Across Membranes

Facilitated fluxes. Although there is an extensive literature on the effects of anesthetics on the transmembrane flows of ions and neutral solutes, generally not much distinction has been made whether the effect is on passive flow, active flow or facilitated flow. From an examination of the literature it appears that the anesthetics can increase or decrease the passive and active flows. The facilitated fluxes, on the other hand, seem to be invariably depressed by anesthetics. This latter generalization has been made by Metcalfe (personal communication) and is also implied in the work of Clayton and Martin (123) who found that the anesthetic alcohols readily depressed the carrier-mediated transport of choline. Facilitated diffusion or carrier-mediated translocation of glucose is inhibited by halothane, methoxyflurane, and ether (237a), butanol (282), triton X-100 (40) and also by various alcohols, urethane and detergents (336). Facilitated transfer of amino acids is inhibited by ethanol (112, 299, 300). It is likely that phosphate permeability is a facilitated process (158), and all anesthetics decrease phosphate transfer (159). The entry of organic anions and cations is passive, rather than facilitated (528, 529), and it would be interesting to know the effects of anesthetics on these species. Other facilitated processes, which are difficult to distinguish from active transport, are also inhibited by anesthetics (111, 216, 225, 301, 374, 536).

There is suggestive evidence that the sodium conductance channel may have characteristics of a facilitated transfer pathway inasmuch as the sodium influx saturates as a function of the external sodium concentration (643, 644; but see also 503). If the generalization that anesthetics inhibit all facilitated transfers is correct, then inhibition of the sodium channel may fall into this category.

Passive permeability. Alcohols reduce the passive permeability of lipid bilayers (see fig. 1E, adapted from 242; see also 618). In biological membranes, the evidence is much less clear. It would be ideal if the anesthetic effects could be studied with rapid-flow methods (236, 527). The time of equilibration of anesthetics across nerve fibers is rather long, of the order of hours (277), complicating the situation. A variety of papers present suggestive evidence that various anesthetics interfere with the permeability to Na^+ and K^+, but it is impossible to figure out from these data whether the drugs are affecting the passive, the active, or the facilitated fluxes of ions (142, 179, 255, 259, 276, 339, 352, 560, 563, 590, 645).

It is known that the entry of Na^+ into erythrocytes is a passive event, and in the presence of Ca^{++} the positively charged amine anesthetics invariably depress passive influx of Na^+ (20, 549). An example of this depression in passive ion permeability is shown in figure 2F. In the absence of Ca^{++} these amine anesthetics increase the membrane permeability. This critical role of Ca^{++} in controlling the anesthetic actions on the biomembrane is also seen in liposomes, wherein the positive anesthetics (procaine, tetracaine *etc.*) *in the presence of* Ca^{++} reduce liposome passive permeability to Na^+ (466); in the absence of Ca^{++}, however, these drugs have very little effect at standard anesthetizing concentrations, and only cause pre-lysis or lysis at higher toxic concentrations (38, 466). The *zeta* potential of the liposomes becomes less negative in the presence of the amine anesthetics (38).

The neutral anesthetics (alcohols), on the other hand, increase the passive leakage of K^+ and Na^+ through lipid membranes (38), erythrocyte membranes (549, 597) and smooth muscle membranes (283).

It does appear as a general conclusion, therefore, that neutral anesthetics increase passive cation diffusion, while positive drugs decrease it. This generalization can be corroborated with the same drug; for example, local anesthetics at pH 6 (where over 98% of the drug is in the charged form) reduce the passive $^{22}Na^+$-influx, while at pH 8 (where 10–60% of the drugs are in neutral form) the local anesthetics increase the passive entry of $^{22}Na^+$ in the erythrocyte (20, 21).

The importance of Ca^{++} in modulating the anesthetic actions on membranes may have to do with the fact that internal Ca^{++} appears to regulate passive permeability (504, 655). The situation must be more complicated than this because chlorpromazine displaces the membrane-bound Ca^{++} while the alcohols and neutral anesthetics increase it.

Anesthetics and pre-lysis. High concentrations of the lipid-soluble anesthetics, concentrations which are within 0.5 of the lytic concentration, invariably cause marked increases in permeability to all solutes, charged and neutral; this concentration range is referred to as the pre-lytic or "pro-lytic" region (28, 95, 145, 252, 281, 284, 467, 479, 510, 542).

XI. On Which Side of the Membrane Do Anesthetics Act?

In order to determine the active form of the dissociating anesthetics (amines and acids), as well as to determine the side of the cell membrane which is most susceptible to anesthetic action, an extensive series of experiments have been

carried out (24, 126, 156, 210, 333, 432, 433, 435, 496–498, 540, 548, 564, 575). It is clearly established that the cytoplasmic aspect of the membrane is sensitive to the action of the positively charged amine form of the anesthetic (435, 540, 575). It also appears that the positive drug may act on the external aspect of the membrane (240a, 540, 575), but this is less clear since the lipid solubility of the quaternary anesthetic may permit the drug to reach the internal aspect of the membrane. Quaternary chlorpromazine is active on both sides of the membrane (240a); the membrane sensitivity to this drug varies with pH (240a).

The neutral form of an anesthetic may act on either aspect of the cell membrane, such as is the case with pentobarbital (432; but see ref. 64).

The careful work of Skou actually suggests that both neutral and charged forms of procaine may be equally effective in producing nerve-conduction block. This conclusion is indicated by the fact that, while the MBC drops from 4.6 mM, to 2.8 mM to 1.3 mM at pH 7, 7.35, and 8, respectively, the total procaine concentrations in the membrane phase remain constant at 0.013 ± 0.001 moles procaine per kg dry membrane; that is, the MBC in the membrane phase is the same at all pH levels (575).

XII. Summary

A diagrammatic summary of the membrane actions of anesthetics and tranquilizers is shown in figure 15. According to the definition of an anesthetic as a drug which directly blocks the membrane action potential, without appreciably affecting the resting potential, a wide variety of lipid-soluble compounds may be considered as anesthetics. Under conditions of general anesthesia the membrane concentration of an anesthetic is 0.003 moles/kg dry membrane, the anesthetic occupying a volume of 0.02% in the membrane phase. Under conditions of local anesthesia the membrane concentration is 0.04 moles/kg membrane, with an occupying volume of 0.3% in the membrane. The partitioning into the membrane is about $\frac{1}{10}$ that of olive oil and about $\frac{1}{5}$ that of octanol. These figures hold for many nerve-blocking drugs, and in order to explain differences in the *in vivo* action of these drugs, other factors must be considered, such as anesthetic sensitization *etc.* The biomembranes expand or swell about 10 times more than the anesthetic volume of occupation in the membrane, 0.4% expansion occuring under conditions of general anesthesia, and 2 to 3% expansion occuring under conditions of local anesthesia. Although the anesthetics electrically stabilize the membrane, they fluidize and disorder the components within the membrane, probably including membrane water. As a consequence of membrane expansion, membrane-associated enzymes and proteins can be either stimulated or inhibited. The pathways for facilitated fluxes of solutes across membranes are invariably depressed, presumably because of the conformation changes brought about by the membrane-expanding anesthetics; the Na^+-conductance channel of the action potential appears to be one of these facilitated pathways. The anesthetic amines displace membrane-bound Ca^{++} and generally depress passive fluxes of cations. The neutral anesthetics generally increase membrane-bound Ca^{++} and generally increase the passive fluxes. The membrane fluidization may explain the en-

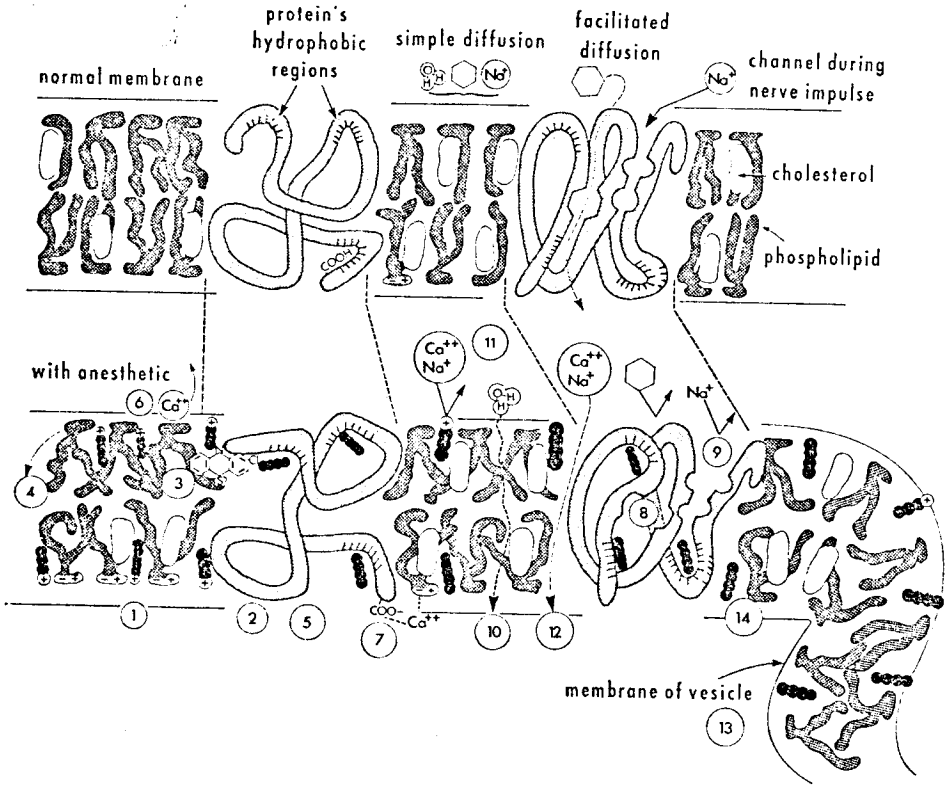

FIG. 15. 1) Drug occupation of membrane by 0.3% in local anesthesia (0.03% in general anesthesia); 2) expansion of membrane by 2% in local anesthesia (0.4% in general anesthesia); membrane pressure alters; 3) increased rotational mobility of membrane units ("fluidization"; disordering); 4) decreased translocation of membrane lipids; 5) activation or inhibition of membrane enzymes, resulting from expansion of membrane protein; 6) displacement of membrane Ca^{++} by anesthetic amines; 7) increase in membrane Ca^{++} by neutral anesthetics; 8) decreased facilitated diffusion of neutral solutes (glucose, choline); 9) *membrane electrostabilization* = decreased facilitated diffusion of ions during nerve impulse (Na^+, K^+); 10) increased passive (Fick) diffusion of neutral solutes (water, urea); 11) anesthetic amines decrease passive (Fick) diffusion of charged solutes (Na^+, PO_4^-, Ca^{++}); 12) neutral anesthetics increase passive (Fick) diffusion of ions (Ca^{++} or Na^+); 13) increased membrane-membrane fusion (*i.e.*, increased neurosecretion); 14) dissociation of lipid-protein complexes (at high anesthetic concentrations).

hanced neurosecretion of membrane-bound materials, by a mechanism of membrane-membrane fusion.

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