ANESTHESIA[1]

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A variety of drugs are used to produce anesthesia, some of them not anesthetic in the strict sense. This review, however, will be concerned only with those agents that induce narcosis, covering in a limited way the basic contributions of the last several years and relating newer developments to the concepts of the past. Several of the adjunct drugs used in anesthesia will have been discussed in this or prior *Annual Reviews*—narcotic analgesics, neuromuscular blockers, certain drugs acting on the autonomic nervous system, sedatives, and local anesthetics.

Although investigation of the pharmacology of anesthetic drugs has burgeoned in the last 15 years, there is a paucity of papers that elucidate basic mechanisms. This is perhaps the result of investigation in the uncontrolled clinical situation, an important area, but one not likely to lead to unassailable conclusions. Nevertheless, the well planned clinical experiment will be cited in this review, the conclusions derived reinforced by data from the experimental animal.

In keeping with the proliferation of scientific writing, there has been a spate of monographs, review articles, and publication of proceedings of workshops and seminars in the field of anesthesia. The best of these will be cited to provide a more extensive bibliography for the reader. For example, the review on anesthesiology by Ngai & Papper (1) is notable for its broad approach and selected references.

Theories of Narcosis and Mechanisms of Anesthesia

Theories of narcosis.—The search continues for a unified concept of narcosis. Following Butler's critical review (2), little additional light was cast on this subject until Pauling (3) and Miller (4) independently announced their molecular theories of general anesthesia. The substance of Pauling's theory is that simple molecules may be linked one to another by hydrogen bonding as the result of instantaneous dipole moment. Clathrates or lattices are formed, the cavities or interstices of which may be occupied by second molecules. For example, chloroform forms a hydrate which at 2°C decomposes to water and liquid chloroform. Xenon on the other hand, a relatively inert gas with anesthetic properties at high pressures, can stabilize a hydrate crystal with a resultant higher temperature of decomposition.

First promulgated in 1959 (5), Pauling's hydrate microcrystal theory was based upon the behavior of an alkylammonium salt with a clathrate structure resembling xenon hydrate. The resemblance of the salt to certain

[1] The survey of the literature pertaining to this review was concluded in March 1965.

amino acid side-chains of proteins suggested that the proteins in the brain could form stable hydrates at body temperature in the presence of an anesthetic agent. Theoretically, the microcrystal thus formed could interfere with ionic mobility, electrical charge, chemical reactions, or enzymatic activity that contribute in some way to the electrical oscillations involved in consciousness. If this were so, anesthetic activity should be proportional to the polarizability of the molecule which in turn influences the stability of hydrate crystals. A striking correlation was found between the narcotizing partial pressures of anesthetics and the partial pressure necessary to form hydrate crystals.

The theory does not apply to the barbiturates which show marked dependence of activity upon molecular structure. Although molecules with strong hydrogen bonds do not fit the theory, diethyl ether probably acts like other nonhydrogen bonding anesthetics by virtue of its electron correlative interaction with water molecules. Thus the hydrate microcrystal theory differs from previous theories in that it involves interaction in the brain with water rather than lipoid molecules. Pauling concluded that any theory based upon van der Waals attraction of anesthetic agents for other molecules would be acceptable inasmuch as the energy of intermolecular attraction is approximately proportional to the polarizability of the anesthetic molecule.

Miller (4) observed that the correlation between the partial pressures necessary for anesthesia and the dissociation pressure of hydrates at 0° C was at least as good as that for the Meyer-Overton lipoid solubility theory. However, in order to determine if crystalline hydrates could form in the body during anesthesia, it would be necessary to extrapolate the data to 37° C. Furthermore, the enthalpies (essentially heat content) calculated for hydrates of different structure, referring to the reaction of a gas in pure water, should be corrected for the effect of salts in interstitial fluid. The corrected anesthetic pressures (fugacities, or ideal vapor pressures) for nitrous oxide and chloroform, 343 and 63 atmospheres respectively, are such as to preclude the use of these drugs in anesthesia or to permit vaporization at ambient temperatures. Despite casting doubt on the hydrate microcrystal theory, Miller believes that the water surrounding a gas molecule is in a more highly ordered state than water in bulk solution, forming a so-called iceberg structure. Such ice clusters may exist in a dynamic condition in liquid water, not all gas molecules being surrounded by icebergs. An attempt was made to calculate the fraction of a surface (whether a membrane, mucopolysaccharide, or other polymer) covered by water which is in a more highly ordered state, using the term "ice cover." At a given temperature the ice cover/water ratio at a surface in the several planes of anesthesia was found to be proportional to the anesthetic partial pressure. Thus, if Miller's model of anesthetic activity is correct, the correlation of anesthetic potency at 37° C and the hydrate dissociation pressure at 0° C can be understood. The analogy to Pauling's theory is made complete by Mil-

ler's suggestion that the ice cover possibly "lowers conductance," "stiffens up the lipoid membranes," or "plugs up the pores of a membrane." Although Miller doubts that microcrystals are formed and stabilized by protein side-chains or that crystals could be formed at all, he suggests that gas-filled icebergs are equivalent to Pauling's microcrystals.

Cherkin & Catchpool (6) working in Pauling's laboratory, followed Miller's suggestion that studies be made in the poikilotherm to establish the validity of the hydrate microcrystal theory. Since the stability of hydrates decreases as the temperature rises, increase of brain temperature should raise the partial pressure required for hydrate formation, hence for anesthesia. Goldfish were acclimated to different temperatures and tested with diethyl ether, chloroform, halothane, and methoxyflurane. The curves obtained showed the dependence upon temperature of the partial pressure of anesthetic agent required to produce a given level of anesthesia. Corresponding changes in enthalpy per mole of anesthetic were calculated and assumed to represent whatever chemical reactions are involved in the anesthetic process. The observed fall in potency with rise in temperature was in accordance with the hydrate microcrystal as well as other physical theories of anesthesia, but not with the Meyer-Overton theory. A strong argument for the latter could, however, be based upon the parallel effects of temperature upon the oil/water distribution ratio. In the case of ether and halothane, however, the ratio rises with temperature but the potency falls.

Featherstone & Muehlbaecher (7) attempted to divert attention from preoccupation with lipoid molecules and suggested that protein molecules may play a role not only in the absorption, distribution, and possibly the metabolism and excretion of anesthetics, but in the mechanism of anesthesia as well. Featherstone et al. (8) demonstrated that the solubility of cyclopropane in blood increased linearly with the concentration of serum albumin, probably as a result of a reversible association of anesthetics with protein, a theory dating back to 1904. Possibly related to this is the demonstration by Lasser, Elizonde-Martel & Granke (9) that sodium acitrozate, a contrast material used in angiographic studies, and known to produce convulsive phenomena when injected into experimental animals in large quantities, may potentiate sodium pentobarbital anesthesia and thereby induce an additional measure of protection against its own central nervous system effects. A host of substances potentiate barbiturate anesthesia in the experimental animal—sedatives, hypnotics, tranquilizers—as well as others that do not supply additive depression. The mechanism has not been elucidated —whether by altered osmotic activity, change in permeability, or additive uncoupling of oxidative phosphorylation. In the case of pentobarbital, since only freely diffusible unbound drug passed the blood-brain barrier into the extracellular fluid, the degree of narcosis may depend upon the percentage of unbound drug that passes into intracellular sites and undergoes binding to tissue protein. Both binding and diffusibility are related to the pH of the

milieu, the pK of a compound, and the degree of dissociation. Lasser hypothesized that potentiation of pentobarbital narcosis by sodium acitrozate is a result of an unfavorable competitive position of pentobarbital with sodium acitrozate for protein binding, not only in hepatic cells and renal excretory cells but in plasma as well. Thus, sustained elevations of total plasma pentobarbital levels, secondary to diminished conjugative and excretory mechanisms, may permit accessibility of more unbound barbiturate to the central nervous system.

In commenting on Lasser's work, Featherstone (10) pointed out that the term "protein binding" must not be loosely used. For example, if the enzyme systems in the liver that metabolize pentobarbital were affected, this would not imply "potentiation." The question is raised whether a greater sensitivity to drugs could be related to lack of protein binding property and whether part of the short-acting properties of drugs such as succinylcholine may not be due to protein binding as suggested by Bovet. Finally, although the effect of proteins relates primarily to transport, the peripheral events may supply a model for those that occur in the central nervous system.

Electrical anesthesia.—The production of anesthesia by electrical current may bear some relationship to the phenomenon of narcosis produced by drugs. Indeed it has been suggested that electrical influences on the brain could involve clathrate formation, thus linking electrical anesthesia to Pauling's and Miller's theories of narcosis. From the pharmacologist's point of view, perfection of techniques of electrical anesthesia may provide the means of inducing narcosis for experimental studies without the complicating effects of anesthetic drugs.

Resurgence of interest in electrical anesthesia led Van Poznak (11) to review the current status of the subject. Although electronarcosis has been of recurrent interest for many years, experimental difficulties still beset this technique. The needs for proper placement of electrodes, for periodic interruption of current, and for a gradual induction were noted as long as ten years ago—as well as certain complications such as localized pain, nystagmus, muscle contractions, and salivation. In contrast to the convulsions produced in electric shock therapy for psychoses, it is the goal of electronarcosis to produce safe and effective near-physiologic sleep during which operation may be performed. In man (12) (the procedure may have been prematurely attempted!) the onset of respiratory obstruction, tonic muscle spasms, and cardiac arrhythmias necessitated the use of sodium thiopental for induction, neuromuscular blockers for relaxation, and antihypertensive medication to counteract the effects of marked increases in the output of catecholamines. In the presence of these many drugs it is not easy to assess the efficacy of electronarcosis.

It is not known whether electrical currents are stimulative or depressant to the central nervous system. An early theory advanced by Burge claimed that volatile inhalation anesthetics caused a reversal of normal elec-

trical polarity in the brain. For electrical anesthesia the alternating currents required range from 700 to 1500 cycles per second through a constant current amplifier producing 25–80 milliamperes. Using the technique employed by Ananèv of Russia (superimposed square waves upon a constant direct current), Smith et al. (13) had some success in animals, although cyanosis, laryngospasm, and skin burns were produced. Higher amperages were necessary in man, with superimposed square waves upon a constant direct current. In summary, electrical anesthesia, as Van Poznak points out, is far from a clinical entity and part of a balanced technique employing physical and chemical agents.

Klemm & O'Leary (14) attempted to characterize electroanesthesia in the cat, to test the hypothesis that previous electroanesthesia influences the response to subsequent experience as suggested by postanesthetic analgesia, and to test the concept that the quality of electroanesthesia can be improved by employing direct current to elevate the wave form above the zero potential line. Optimal anesthesia with the least amount of current was produced by those wave forms with the smallest pulse-duration period ratios. Elevation of the wave above baseline did not reduce untoward reactions, both motor activity and local burns being produced. However, laparotomy could be satisfactorily performed in the cat, but only with supportive drugs and tracheal intubation; previous electrical anesthesia did indeed influence the response to subsequent delivery of current. There was variability in the persistence of pain reflexes suggesting that the mechanism of analgesia is different from that produced by drugs, and a delay in the recovery of normal function occurred. In conclusion, the pulse-duration period ratio data suggest that this determines the effectiveness; that narcosis is due to the stimulating rather than depressant properties of wave forms (Van Harreveld 1942); that stimuli with the smallest ratios are most effective, but, independent of ratio, frequency may exert an influence of its own.

Electrical activity of the brain.—In a sense the effects of anesthetics on the electrical activity of the brain are allied to the basic mechanism of narcosis. Recent work dates back to Magoun's demonstration that ascending sensory systems in the core of the midbrain and medially placed nonspecific hypothalamic nuclei exert a marked influence on the state of consciousness. Studies done in animals with implanted electrodes and recording of visually evoked responses demonstrated the susceptibility of the midline nonspecific system to the depressant effect of barbiturates, although the phenomenon is not peculiar to the visual system. Thus, any drug that depresses this system will produce unconsciousness. Killam (15) reviewed the actions of many types of drugs on the brain stem reticulum formation. Brazier (16) pointed out that several of the older concepts of anesthesia are, therefore, no longer tenable—such that anesthetics impair consciousness by preventing afferent impulses from reaching the cortex or that anesthetics exert an influence horizontally from level to level on the succession of phylogenetically required areas of the brain.

Brazier (17) pioneered in the use, both in animals and man, of computer techniques based upon the average, over many responses, of electrical activity time-locked to a stimulus; in this way unrelated background activity gradually averages out. With this method, the effect of anesthetics on the classical sensory system (in addition to the nonspecific afferent system) was studied as well as the phylogenetically older limbic system. Brazier showed that the former is extremely resistant to anesthetic depression whereas the hippocampal system in particular (concerned in message storage and retrieval) is vulnerable to the action of anesthetics. Using occipital leads Cigánek (18) demonstrated the modification by sodium thiopental of visually evoked responses in man with no effect on the primary complex, and enhancement of the late negative waves in the secondary response. This work and that of Brazier showed that modification of the visually evoked response by anesthetics is dependent both on the depth of anesthesia and on the site from which responses are recorded.

Domino, Corssen & Sweet (19), using highly sensitive electronic averaging techniques, studied the effect of preanesthetic medication and most of the commonly used general anesthetic agents on the visually evoked response. Although studies such as these cast no new light on the mechanism of general anesthesia, they showed that the cortex responds to visual afferents remarkably well during light surgical anesthesia; also found was an enhancement of the visually evoked response, long thought to occur in the second or excitement stage of anesthesia. Confirmatory of clinical impression, cyclopropane and ether were especially effective in markedly altering and depressing the average visually evoked response at various planes while thiamylal was effective only in high doses, with marked flattening of the EEG to a burst suppression pattern. Nitrous oxide, halothane, and methoxyflurane, rather than obliterating the response enhanced it; in the latter case cardiac depression prevented the deepening of anesthesia to the point where the response could have been eliminated. EEG techniques were likewise employed by Domino et al. (20) to study the effect of xenon at elevated pressures in the dog. This work again demonstrated that a wide variety of seemingly unrelated chemical agents produce overtly a similar state of general anesthesia, and strengthened the hypothesis of a physical mechanism underlying narcosis. Abrahamian et al. (21), likewise using automatic averaging techniques in man, studied the evoked responses in post-Rolandic sites (the points of shortest latency) following application of rectangular pulse waves to the median nerve. As previously shown in animals, thiopental abolished what were interpreted to be the extraleminiscal components of the evoked responses, with a differential sensitivity of the various subdivisions of the extraleminiscal pathways.

Despite these several observations, the precise relationship of drug-induced changes in evoked potentials to the clinical manifestation of general anesthesia requires further elucidation.

Anesthetic potency.—Although closely related to the general aspects of narcosis, anesthetic potency is not easily defined. In this sphere, Chenoweth

& McCarty (22) discussed the mechanisms of the pharmacophoric effects of halogenation. Merkel & Eger (23) approached the problem of potency in a comparative study of halothane and halopropane anesthesia with a method for determining equipotency. The minimal anesthetic concentration (MAC) of these anesthetics was defined as the alveolar concentration, in a steady state, which could prevent movement in the dog in response to clamping the tail or stimulation of the mucous membrane with an electrical current. With the MAC defined as 1.0, anesthetic depth could then be defined as the ratio of the alveolar concentration to the MAC. Under suitably controlled conditions the MAC for both halothane and halopropane was found to be remarkably constant during both spontaneous and controlled pulmonary ventilation. Halothane was more potent, with an MAC of $0.55 \pm .09$ per cent in contrast to halopropane with $0.80 \pm .08$ per cent. Although the concentration of halothane could be raised consistently to greater multiples of MAC, increase in halopropane led to apnea, and the need for controlled ventilation which in turn reached a limit owing to the development of hypotension. This reproducible method of determining potency may be contrasted with the difficulty in using physiological parameters as an indication of depth, or the EEG which varies according to the agent used. The partial pressure of the anesthetic in the alveoli may be considered a constant, and indicative of the partial pressure in the central nervous system. However, such potency figures must be carefully determined because of the differences in solubility in blood of the several anesthetics and the need to attain equilibration. Another theoretical application of the MAC is possible if anesthetic potency can be equated with the oil/gas partition coefficient. Here MAC does not conform to the solubility data since halopropane, with an oil/gas ratio of 323, is less potent than halothane, with a solubility coefficient of 224. Furthermore, if potency is considered to be in inverse ratio to the saturated vapor pressure, these agents do not follow the pattern insofar as MAC is concerned.

Saidman & Eger (24) measured the effect of nitrous oxide and of narcotic premedication on the alveolar concentrations of halothane required for anesthesia. The concentrations obtained were compared to the MAC obtained without nitrous oxide or narcotics. Nitrous oxide in 70 to 75 per cent concentrations was effective in lowering MAC to approximately 60 per cent, absolute reduction from 0.75 to 0.45. This could have been predicted on theoretical grounds by multiplying the MAC times the oil/gas solubility coefficient for each agent (a constant for any anesthetic agent) and calculating the ratio of the two figures. There was only a 7 per cent reduction in MAC following the use of morphine in quantities ranging from 8 to 15 mg.

Uptake and Distribution of Anesthetics

The uptake and distribution of anesthetics have long been the focus of research. Improved methodology has led to reaffirmation and refinement of the general tenets established by Haggard (25) and Kety (26) many years

ago. The result has been the establishment, on a physical and physiological foundation, of a firm basis for the safe administration of anesthetics, and for the planning and synthesis of new compounds. Recent work is cited in the proceedings of a National Research Council symposium (*27*) and in another symposium on the pharmacokinetics of inhalation anesthetic agents (*28*). Of particular interest in the former is a discussion of the role of pulmonary factors in uptake, the quantitative prediction of anesthetic concentrations, the construction of electrical analogues that can be used as teaching models, and the derivation of mathematical models of uptake and distribution.

In a mathematical model, Eger (*29*) assumed that there is a constant alveolar tension of anesthetic, and circulation to the tissues which he classified into four groups: VRG, a vessel rich group (the brain, heart, kidneys, and hepatoportal system); MG, a muscle group; FG, a fatty group; and VPG, the vessel poor group consisting of bone, cartilage, ligament, and tendon. The volumes assigned to these groups were 6.0, 33.0, 14.5, and 12.5 per cent of the body mass, respectively. Perfusion rates were 4.5, 1.1, 0.32, and 0.09 liters per minute. Employing these figures, the rate of uptake of an anesthetic could be calculated on the basis of the blood and tissue solubility coefficients for each agent.

Reactivity of anesthetics.—Despite the long-held belief that inhalation anesthetic agents are chemically inert, a review by Van Dyke & Chenoweth (30) indicates that this is not so. Prior failure to investigate this aspect probably relates to the belief in physical rather than chemical theories of narcosis, to lack of sensitivity of analytical methods, and more importantly to the fact that little metabolic degradation could be expected after inhalation of a single dose of anesthetic and its rapid elimination. Furthermore, inhalation agents are given continuously and are distributed widely to the body compartments and to organs wherein metabolism may not take place. With the use of radioactive isotopes, 1.5–12.0 per cent of most anesthetics investigated have been found to be converted to carbon dioxide. A basic tenet in studies of degradation is that the compound examined must be chemically pure. Conversion takes place in microsomes where reduced nicotinamide adenine dinucleotide phosphate (NADPH) is required as a cofactor in H^+ ion transfer. The microsomes involved are probably subject to the same variation in quantity and activity as other microsomes that are active in metabolism of drugs.

Ethylene is converted to ^{14}C-carbon dioxide and labeled urinary products (30); and it is interesting that ethylene is produced *per primum in vitro* by hepatic mitochondria. Both cyclopropane and diethyl ether are converted to carbon dioxide. The mechanism for ether probably involves the addition of a hydroxyl group to the ether linkage to form acetaldehyde and ethanol. Chloroform is converted to carbon dioxide both *in vivo* and *in vitro* and it is noteworthy that carbon tetrachloride is metabolized to chloroform *in vivo* and *in vitro* in liver slices. It has long been known that tri-

chloroethylene appears in the form of urinary metabolites, as trichloroacetic acid, trichloroethanol, and inorganic chloride, and as *trans*-1-2-dichloroethylene in expired air. Halothane labeled as 1-^{14}C and ^{36}Cl is metabolized in rats, both ***in vivo*** and ***in vitro***. Presumptive evidence for breakdown of halothane in man has been shown by the appearance of bromine in the urine (31); trichloroacetic acid is also a metabolite. In conformity with the original concept of inertness, the carbon-fluorine bond is broken enzymatically in microsomes, a reaction requiring NADPH and oxygen with the major products—chlorine, bromine, and trifluoroacetic acid. The microsomes involved are increased by pretreatment with a known microsomal inducer, phenobarbital, to increase the urinary end products two to four times. Trifluoroethylvinyl ether, or fluoroxene, is likewise broken down. Even xenon has been found to enter into chemical reactions. Finally, it is suggested that nitrous oxide, the only inorganic inhalation agent, may be a chemically reactive substance.

The implication of all this is that metabolic transformation places inhalation anesthetics in the same position as other drugs. While metabolism probably does not play a major role in maintenance of anesthesia, because anesthetics are given more or less continually, these findings call for a reevaluation of certain aspects of the newer theories of anesthesia. There is the suggestion that the ability to undergo metabolism parallels potency. Lastly, there are implications in the possible toxic properties of anesthetics, if metabolism leads to toxification rather than detoxification; this is of extreme importance in the determination of the hepatotoxicity of halogenated anesthetics.

Solubility coefficients.—Solubility is the prime determinant of uptake and distribution, the characteristic which distinguishes one anesthetic from the other, the property which defines the rapidity of induction and recovery and, finally, anesthetic potency itself (32). Those factors which influence the solubility coefficients are the anesthetic substance itself and the solvent (with solubility greatest in lipids, less in protein, and least in aqueous media). Electrolytes diminish the solvent capacity by means of a salting-out process. Since biological media are complex, prediction of solubility is not possible as a rule. For example, there is a differential solubility in the gray and white matter of the brain, while solubility increases with decreasing temperature both in aqueous and oily media. The final determinant of solubility of a gas is the partial pressure as reflected by Henry's law.

The table of solubility coefficients compiled by Eger & Larson (32) presents recent data, with figures hitherto not available for xenon, fluoroxene, halothane, methoxyflurane, trichloroethylene, and divinyl ether. The least soluble agent in blood is ethylene, the most soluble is ether, and the more soluble substances are trichloroethylene, chloroform, and methoxyflurane. Slightly soluble agents are cyclopropane and nitrous oxide, with halothane intermediate between lesser and great solubility. As a rule, solubility in blood lies between that of water and oil. If the difference in solubility be-

tween oil and water is small, the values for blood and water are practically identical; with a greater solubility in oil there is a rise in the blood coefficient as compared to water. Tissue solubilities generally range between those of blood and oil, in general approximate a value of one. However, halothane and methoxyflurane show a greater solubility in tissues.

A close correlation between potency and the oil/gas coefficient has once more been demonstrated (32). Using the MAC for halothane 0.9 per cent, ether 3 per cent, and cyclopropane 18 per cent, a constant is derived by multiplying MAC times the oil/gas coefficient: this proves to be 212 for halothane, 185 for ether, and 202 for cyclopropane. Thus, in general, potency can be predicted by employing an average constant of 200 and the oil/gas coefficient.

Factors influencing uptake of inhalation agents.—Prior studies determined anesthetic uptake at a constant inspired tension, usually low so as to avoid physiological effects of the anesthetic, and the equilibrium state was defined as the rate at which the expired tension approached the inspired tension of anesthetic. Eger & Guadagni (33) measured the uptake of halothane in man at a constant alveolar rather than a constant inspired tension. Under controlled physiologic conditions alveolar concentration was held at approximately 0.8 per cent, the minimum anesthetic concentration, by constantly adjusting the inspired tension. Uptake was defined as the inspired minus the expired alveolar concentrations times the alveolar minute volume of ventilation. The data obtained were compared with those calculated by means of the mathematical model described above. Although there was considerable variation among subjects, the experimental and theoretical curves were parallel. Uptake of vapor declined rapidly at first, then more slowly. If the alveolar concentration can be considered equal to that of the brain, the figures obtained provide an accurate measure of how much halothane is required to maintain a subject in a constant light level of anesthesia. The same equations were used to predict uptake at a constant inspired tension and the data compared to the results found by Sechzer, Linde & Dripps (34) in an earlier study on halothane. Change in uptake with time is much greater at constant alveolar than at constant inspired tension, the difference being related to the solubility in blood. Agents with the greatest solubility show the greatest differences between the two techniques. The same technique was used by Eger (35) to measure uptake of methoxyflurane, a highly soluble agent, comparing constant alveolar and inspired concentrations. Once more, predicted and measured curves were fairly close and the curves for inspired and alveolar concentration were quite different, as noted with halothane.

Both Haggard and Kety had assumed in their mathematical computations that when a soluble inert gas is inspired, the rate at which the alveolar concentration (F_E) of that gas approaches the inspired (F_I) concentration is independent of the inspired concentration. However, Eger (36) showed that this was not the case; the higher the concentration the more rapid the change

in the ratio, F_E/F_I. Two corollaries of this observation are offered. (*a*) At a theoretical 100 per cent inspired concentration, with a constant alveolar minute volume, "wash in" curves are identical for soluble and insoluble gases. (*b*) Gases with the greatest solubilities show the greatest variations as inspired concentrations are altered.

Epstein et al. (37) measured the influence of concentration on the uptake of a single gas. The concentration effect is best described in the following manner. Absorption of a gas creates a potential subatmospheric intrapulmonary pressure which results in an augmented tracheal inflow, which is added to the no longer constant inspiratory ventilation. There is a more rapid approach to equilibrium in the alveoli—the higher the concentration, the larger the total volume of gas absorbed and therefore the greater the augmentation of inflow. Experimental confirmation for this was obtained with nitrous oxide although the concentration effect should be greater in the case of more soluble agents. However, the latter, being more potent, are usually given in low concentrations, and the concentration effect can only be small. Nevertheless, when nitrous oxide was given to dogs with the more soluble halothane, the uptake of halothane at a constant inspired concentration of 1 per cent was more rapid—more so with mixtures containing 70 per cent than 10 per cent nitrous oxide. This "second gas" effect presumably occurs for other gases given in mixtures and includes the respiratory gases, oxygen and carbon dioxide.

Passage of drugs, including anesthetics, across body membranes was the subject of a review by Schanker (38). There have been only a few studies on gas uptake in organs other than the brain which, from the anesthetic standpoint, is most important. Since the kinetics of cerebral uptake had hitherto not been carefully studied, Alexander and his co-workers (39) measured the cerebral uptake of trace quantities of ^{85}Kr and a subanesthetic concentration (15 per cent) of nitrous oxide. While this should best be done during induction with either agent, alterations may occur because of changes in respiration. Hence the study was performed during a constant level of light halothane anesthesia, with the arterial P_{CO_2} varied to achieve hypo-, normo-, or hypercarbia. At three different levels of cerebral blood flow as created by changes in arterial CO_2 concentration, with administration of ^{85}Kr in a nonrebreathing system, arterial concentration reached its final value in seven minutes, but the jugular concentration lagged behind. Arteriovenous equilibrium was not achieved during a 15 minute period of measurement. Cerebral Kr concentration approached its final value considerably more slowly than the jugular venous blood concentration. At ten minutes, cerebral Kr content was 83.7 per cent of its final value, while the jugular venous blood had reached 94.9 per cent. The rate of cerebral uptake for nitrous oxide was approximately the same. As previously suggested, the rate of inert gas uptake by the brain is influenced by cardiac output, cerebral blood flow, alveolar ventilation, and solubility of the gas in blood and brain. This study showed that uptake of gases is essentially a

flow rather than a diffusion-limited process. As cerebral blood flow decreased below 44 ml per min per 100 g, the rate of brain equilibration dedecreased sharply; elevated flows increased the rate of approach to equilibrium. Since the curve of uptake (relating cerebral blood flow to rate of saturation) is hyperbolic, an increase in cerebral flow changes the rate of equilibration less than a decrease in cerebral blood flow. The slow rate of brain saturation as demonstrated here is at variance with earlier work, but there is reason to believe that the whole brain behaves as a two-compartmental system, that cerebral blood flow is heterogeneous varying from region to region, the white matter more slowly perfused. From a clinical point of view, hastening the arterial uptake of an anesthetic by hyperventilation and removal of carbon dioxide would decrease the cerebral blood flow and negate or reverse the effect of the extra ventilation. However, hyperventilation with 4 per cent carbon dioxide could increase both arterial uptake and cerebral blood flow, an advantage in the case of a more soluble agent.

Intravenous agents.—Mark (40) reviewed recent information on the metabolism of barbiturates in man. Methohexital was examined by Brand and his co-workers (41) with regard to physiologic disposition and explanation of the behavior in man. This oxybarbiturate is of the ultra short-acting variety, similar to the thiobarbiturates, but reputedly offering a quicker recovery and fewer long-lasting depressant effects. After intravenous injection, the plasma concentration was similar to that of thiopental, the early rapid decline representing a shift to tissues and the later slow decay curve indicative of biotransformation. Concentration in fat increased with time, reaching two to six times the plasma concentration in two to four hours. Methohexital was transformed at a rate ranging from 15 to 19 per cent per hour in comparison to 20 per cent for methitural and 15 per cent for thiopental. About 73 per cent of methohexital was bound to the nondiffusible constituents of plasma. Nevertheless, rapid passage into the brain was shown by loss of consciousness and development of characteristic EEG changes within 15 to 20 seconds of intravenous injection. It seems to be about 2 to 2.5 times more potent than thiopental. Although the oil/water solubility coefficient of methohexital is 65, suggesting a lesser potency than thiopental with a coefficient of 89, the finding of 76 per cent of methohexital in the un-ionized state at a pH of 7.4 in contrast to 61 per cent of thiopental implies that more methohexital is available for transfer across the blood-brain barrier. There is little difference in binding to plasma protein between the two short-acting barbiturates. Less methohexital than thiopental is present in fat at a given time, perhaps allowing more to be present in plasma and available, therefore, for biotransformation.

Dal Santo (42) studied the kinetics of distribution of ^{14}C-dimethyl *d*-tubocurarine. Following administration of trace amounts to man and dog, about 0.8 per cent of the drug was present in plasma after 15 hours, about 85 per cent having been excreted in the urine, and 14 per cent was still present in extramuscular compartments. Chromatographic analysis showed

that the compound apparently remains unchanged in the body of the dog while a minute amount, about 10^{-5} of the administered dose, crossed the blood-brain barrier and appeared in the cerebrospinal fluid. As in the case of the barbiturates, the exponential plasma decay curve showed an initial descent corresponding to transfer to interstitial and intracellular compartments. The subsequent gradual descent of the curve mirrored the ascending curve of urinary excretion. The slope of the curve explains the duration of action of a single injection of curare, about 30 minutes, corresponding reasonably well with the phase of rapid disappearance from plasma and peak passage into tissue compartments. At 15 hours, the data showing 85 per cent of the curare recovered, 0.8 per cent in plasma and the remainder, about 14 per cent, still unaccounted for, probably explain the need for lesser amounts of drug upon subsequent injection.

Cohen, Corbascio & Fleischli (43) likewise studied the distribution and fate of *d*-tubocurarine. The drug was given to dogs (*a*) in small amounts to produce paralysis and (*b*) in larger quantities to study saturation of depots. Several nephrectomized dogs were studied and tissue biopsies were taken from patients. Plasma concentrations were studied spectrophotometrically. Pulmonary ventilation was controlled to provide normal Po_2 and Pco_2, the ECG monitored and hypotension prevented by administration of dimethyl pyrophosphate, a ganglionic stimulator, to the group given larger quantities. Pentobarbital or thiopental and nitrous oxide were the anesthetics employed. The usual plasma decay curve was obtained with a corresponding rise in muscle content, hepatic concentration, and urinary excretion. Renal concentration rose more slowly than in muscle or liver. The role of the kidneys was shown in the nephrectomized animals where, after distribution to the body compartments, the plasma curve reached an asymptote. However, subsequent metabolic transformation caused a further decline. There was a slight difference in the rate of renal excretion between the two techniques. With the higher dose of *d*-tubocurarine the distribution curve was initially the same but the rate of descent less. Liver and muscle accumulated more curare while the constancy of plasma concentration suggested saturation. The data obtained from biopsies in man were similar to those of the dog. Protein binding occurred, with the usual influence of changes in pH. With minimal paralyzing doses the concentration in muscle closely paralleled that of plasma. The absence of *d*-tubocurarine in fat was expected since the compound is poorly soluble in organic solvents. Additional data from various sources also suggest that there is a placental as well as a blood-brain barrier to passage of *d*-tubocurarine (44).

Anesthetic Effect on Cells and Intermediary Metabolism

Advances in this field were reported in the proceedings of a conference on this subject (45).

Cellular processes.—Chance & Hollunger (46) reported on the salient features of the structure and function of the oxidative phosphorylation sys-

tem wherein anesthetics may exert an effect. Herein the mitochondrion is of special interest in problems of anesthesia; electron-microscope studies led to identification of probable enzymatic sites on the mitochondrial membrane. In the respiratory chain oxygen is reduced to water as a result of a flow of electrons. Thus there are two general sites upon which anesthetics can exert an inhibitory action, one being a point at which electrons are prevented from flowing—at the terminal enzymes, for example, cytochrome. Of greater importance, however, is the observation that inhibitors such as the oxybarbiturates act via reactions which siphon energy from the respiratory chain as well as resulting in inhibition of electron flow. Since a number of the components of the respiratory chain can be identified, it is possible to detect the pile-up of reduced enzyme on the substrate side of an inhibition site, and depletion of the reduced forms of the enzymes on the oxygen side of the inhibition site. This is called the crossover point. In phosphorylating mitochondrial preparations of the rat liver, the crossover site, as illustrated by barbital, was found between NADH and flavin. Since this is an important energy conservation site of the respiratory chain, the suggestion is made that oxybarbiturates act not on electron transfer, but upon the energy transfer reactions of intact mitochondria.

Quastel (47) continued his studies on the effect of anesthetics on carbohydrate metabolism in the brain, *in vitro*. Studies on cation, or electrically stimulated brain slices, and on brain mitochondria showed that anesthetics at low concentration bring about inhibition of certain respiratory processes. Since the respiratory rate of tissues *in vitro* is about one half of that *in vivo*, the respiratory rate was increased to normal levels by increasing potassium in a sodium medium or sodium in a potassium medium, or by decreasing calcium. This stimulation occurs only in brain slices, not homogenates or minces. The stimulation of respiration consists of an increased turnover of the citric acid cycle as it is highly sensitive to malonate. Both forms of stimulation are highly sensitive to the barbiturates and other anesthetics which suppress metabolism activated both by potassium and sodium. The explanation of this effect may be found in: (*a*) inhibition of electron and energy transfer in mitochondrial metabolism; (*b*) inhibition of the cation movements at the neuronal membrane affecting the ratio of adenosine diphosphate (ADP): adenosine triphosphate (ATP) in the neuron, and thereby the rate of mitochondrial respiration which is partly controlled by the ADP level. The barbiturate, amobarbital, and the hypnotic, chlorobutanol, suppress the rate of oxidation of reduced nicotinamide adenine dinucleotide ($NADH_2$) by the cytochrome system. The latter finding supports the conclusions of Michaelis & Quastel in 1941, that the site of action of anesthetics is at a process playing an intermediate role between cytochrome oxidase and a flavoprotein concerned with the oxidation of $NADH_2$. Since biological oxidation of $NADH_2$ is controlled by phosphorylation of ADP to ADT, it follows that anesthetics are also inhibitory to oxidative phosphorylation. The suppression of oxidation of $NADH_2$ by amobarbital has the

double effect of suppressing the citric acid cycle (as the rate of this depends upon the supply of acetyl CoA which is formed by oxidation of pyruvate by NAD)—and the formation of ATP. At low concentrations, barbiturates suppress the oxidative uptake of phosphate. Interference with ATP synthesis is shown by their suppression of synthesis of acetylcholine and an inhibitory effect on incorporation of ^{32}P (from phosphate) into phosphoproteins or organic phosphorous compounds in cat brain slices. Amobarbital also suppresses biosynthesis of glutamine, a reaction which is ATP-dependent. These studies suggest that one way an anesthetic can suppress functional activity of a neuron is by suppression of rate of biosynthesis of substances needed for neuronal function, that require mitochondrial ATP (or other high energy phosphates) for their formation.

Hepatic metabolism.—Brauer (48) examined the metabolic effects of anesthetics on the liver of the rat perfused with whole blood. The greater number of experiments were performed with chloroform and with carbon tetrachloride, a known hepatotoxin. Less than 2 per cent chloroform inhibits biliary secretion, and recovery of biliary formation is poor. After attainment of a baseline with a constant blood flow, chloroform causes vasodilation. Chloroform accelerates a natural fall in glycogen levels in these preparations and a rise in blood glucose levels which, initially at least, is dose dependent. Although hypoxia does this too, the degree of glycogen depletion is much less. A marked decrease in oxygen consumption, not dose related, was observed to be not attributable to a decrease in oxygen delivery but rather to an effect on the metabolic apparatus itself. There is also a fall in pH as a reflection of an increase in lactate level. Brauer does not calculate excess lactate levels for the liver because he believes that the metabolites in blood may not be representative of tissue levels. These biochemical events are paralleled by the morphologic changes seen in electron-microscopy. There is a breakdown of the endoplasmic reticulum and a formation of vacuoles. The question arises as to whether these changes represent irreversible cell injury.

The question was raised as to how far these changes are representative of other anesthetics. Diethyl ether produces some of the changes noted above, but they are reversible and there is no decrease in oxygen consumption as noted with chloroform. Perhaps the only difference between chloroform and other agents is that changes owing to chloroform are irreversible. It is interesting that high oxygen tensions protect the liver against the toxic effects of carbon tetrachloride whereas the centrilobular location of the chloroform lesion (thought to be due to diminished oxygen tension) is not affected by reverse perfusion of the liver; hence the zonal location of lesions may indicate a biochemical rather than oxygen gradient.

Epstein et al. (49) studied the comparative effects of cyclopropane and halothane on the splanchnic circulation and metabolism in man. The work was done in volunteers, the body temperature and P_{CO_2} held constant and the anesthetics given at a constant inspired tension, 18 per cent for cyclo-

propane and 1.2 per cent for halothane. Cyclopropane increased the perfusion pressure but reduced splanchnic blood flow through an increase in peripheral resistance. This was reflected in a reduced rate of clearance of indo-cyanine dye and the appearance of excess lactate. However, splanchnic oxygen consumption and hepatic venous oxygen tensions were inconsistently affected. The administration of hexamethonium changed the picture so that perfusion returned to normal, oxygen consumption transiently increased, clearance of dye and venous oxygen tensions were unchanged, and the excess lactate reduced. These alterations suggest that certain of the metabolic changes including the appearance of excess lactate were the result of sympathetic nervous activity (although lactate should increase in proportion to pyruvate). In contrast to cyclopropane, halothane diminished perfusion pressure and thereby hepatic blood flow; dye extraction was reduced and the venous oxygen tension diminished, with no effect on the overall oxygen consumption and no liberation of excess lactate. There are two possible explanations for these contrasting and seemingly contradictory findings. If one can accept the validity of data based on calculation of excess lactate, the change in lactate observed with cyclopropane may not be an evidence of hypoxia, but a metabolic effect of sympathetic action. The use of sympathetic β-blockers could be elucidatory here. The other possibility is that the circulation under cyclopropane is functionally different, that these measurements represent hypoxia, that cyclopropane restricts the circulation and as flow diminishes the diffusion distances become greater and the tissues suffer anoxia.

Cerebral metabolism.—Cohen et al. (50) assayed the effect of halothane on cerebral carbohydrate metabolism in man. Prior studies had shown that during nitrous oxide or halothane anesthesia there was either no change, or only a slight change in the rate of cerebral oxygen consumption. At a normal P_{CO_2}, changes in glucose consumption paralleled the changes in oxygen consumption. Additional studies were then performed to partition the fate of glucose into aerobic and anaerobic pathways of metabolism by calculation of excess lactate as indicated by appearance of lactate and pyruvate in arterial and jugular venous blood. Changes were expressed in terms of aerobic or anaerobic indices. During thiopental-nitrous oxide or halothane anesthesia at normocarbia, regardless of the overall rate of oxygen or glucose utilization, pathways of carbohydrate metabolism were unchanged. However, the effect of excessive pulmonary ventilation produced interesting effects, as it affected the pH and P_{CO_2} of arterial blood. In some individuals under nitrous oxide anesthesia with P_{CO_2} reduced to 15 mm Hg, there was an increase in lactate production and in the anaerobic metabolic index; this was associated with signs of hypoxia in the EEG, although completely reversible. Such changes were not observed above a P_{CO_2} of 25 mm Hg. With halothane there was no evidence of anaerobiosis at 25 mm Hg. A possible explanation for the anaerobiosis during hypercarbia is the incorporation of glucose into alternate metabolic pathways, perhaps

protein synthesis or fatty acid formation. This could lower the ratio of oxygen consumed to glucose transformed. Or during hypocarbia, oxygen consumption could be contributing to the oxidation of other substances besides glucose. In either case, however, only 10 per cent of the glucose metabolized would be involved.

Myocardial metabolism.—Galla et al. studied the effects of ether (51) on myocardial metabolism in the dog in an attempt to discover the reasons for myocardial depression produced by this anesthetic. During ether anesthesia, as previously shown, arterial concentrations of glucose, lactate, and pyruvate rose while nonesterified fatty acids fell. Myocardial extraction of these substances was a linear function of the arterial concentration, except in the case of glucose where the rate of extraction decreased at higher arterial levels. A measured rise in RQ suggested that carbohydrate substances extracted were being oxidized. In general, this was also the pattern found in the unanesthetized animal. However, glucose extraction in the unanesthetized animal exceeded 20 mg per cent when the arterial concentration was over 120 mg per cent, but with ether, extraction was considerably less than 20 mg per cent at this arterial level. Ether, therefore, seemed to alter glucose extraction.

Anesthetics and the Circulation

Research in anesthesia has focused largely on the circulation in contrast to the relatively few studies on respiration or the neurophysiological aspects of anesthesia. Much of the latest information on circulatory studies has appeared in monograph form (52), the proceedings of a conference on this subject.

Central neural effects of anesthetics.—Although it has been known that anesthetics exert profound effects on the autonomic nervous system, studies of the central actions have been lacking. The action of cyclopropane in raising blood pressure, maintaining the cardiac output, causing release of norepinephrine, and increasing myocardial irritability led Price et al. (53) to study the hemodynamic and central nervous actions of cyclopropane in the dog. Upon perfusion of the dog's head (with only neural connection to the body) with blood containing cyclopropane, there was elevation of mean arterial blood pressure, increase in pulse rate, and increase in peripheral circulating catecholamines. When the body was perfused, the mean arterial blood pressure declined. The former response persisted until section of the brain stem was made at a level just rostral to the medulla oblongata. In contrast to earlier studies (54) which showed sensitization of the carotid baroreceptors after perfusion with cyclopropane, the current experiment showed no increase in sensitivity. In addition, cyclopropane circulated to the head diminished the depressor response brought about by carotid sinus distention, a response not altered by section of the vagi; the depressor response induced by central vagal stimulation was also reduced by cyclopropane circulated to the head. During these maneuvers, the peripheral circula-

tion was, as usual, responsive to administration of norepinephrine. Cyclopropane did not exaggerate the peripheral circulatory depressant responses to phentolamine or camphorsulfonate. It was apparent therefore that the usually observed increase in sympathetic activity with cyclopropane was not the result of a reflex response to peripheral vascular depression. Rather, contrasting central and peripheral effects were shown and the conclusion drawn that cyclopropane probably inhibits the depressor neurons in the medulla. This action does not account for all of the circulatory phenomena noted during cyclopropane anesthesia in the intact preparation.

The central effects of halothane were likewise studied in the dog (55); a slightly different preparation was used. In contrast to cyclopropane, central circulation of halothane brought about a decrease in mean arterial blood pressure, heart rate, myocardial contractile force, and pulse pressure, which could not be attributed to an analgesic effect of the agent or to deterioration of the specimen. There was, however, a reduced response to carotid sinus stimulation produced by occlusion or distention. Since vagal blockade did not modify these responses, the conclusion was drawn that halothane reduces sympathetic activity or outflow. This action permits halothane to exert a direct depressant action peripherally without compensatory autonomic sympathetic activity. In support of this hypothesis was the demonstration that halothane reduced the responsiveness of both cardiac and vascular smooth muscle to sympathetic mediators.

Two final experiments were performed to substantiate the conclusions concerning the vascular effects of cyclopropane and halothane. First, in vagotomized decerebrated dogs the medulla oblongata was explored for maximal pressor or depressor responses to direct electrical stimulation (56). After the most responsive areas had been located, the effects of cyclopropane, halothane, and procaine were compared by direct injection in a standard volume of saline. All three agents caused reversible depression of responses from pressor and depressor areas. Although halothane and procaine were approximately equal in effect, cyclopropane had a disproportionately lesser effect on pressor representations. When halothane and cyclopropane were compared in equinarcotic concentrations, halothane depressed the pressor response to a degree twice that of cyclopropane.

The second confirmatory experiment involved study of the effect of halothane on systemic baroreceptors (57). It had been suggested that baroreceptor sensitization may be responsible for arterial hypotension observed during induction of anesthesia with various volatile anesthetics. Therefore in cats under chloralose or urethane anesthesia the carotid sinus was isolated, the sensory nerve dissected free, and the sinus distended with static pressures. The rate of discharge over the afferent nerve was then recorded at constant distention. During inhalation of 1.2 per cent halothane, an initial increase in baroreceptor sensitivity was found, averaging 15 per cent. However, as inhalation of halothane was continued, there was a return to normal or below discharge levels.

Peripheral Circulatory Effects of Anesthetics

Myocardial function.—Morrow reviewed recent approaches to the study of the effects of anesthetics on ventricular function (58). In these studies emphasis has shifted from mere measurement of cardiac output to more refined estimates of the function of the heart as a pump. Preparations and techniques have included the Starling heart-lung preparation, measurement of maximal isometric systolic tension with the strain gauge arch, the relationship between ventricular stroke work and diastolic ventricular fiber length (ventricular function curves), and the assessment of changes in ventricular power. It is not possible to encompass all the work done in this field or to discuss theoretical implications in a general review of this nature. Some of the trends, however, may be indicated.

Earlier work demonstrated the depressant effect of diethyl ether, cyclopropane, nitrous oxide, and thiopental on ventricular performance curves, indicated by changes in the slope of the curves relating cardiac output to right atrial pressure (59). In the heart-lung preparation of the dog, Flacke & Alper (60) showed that halothane in concentrations greater than 1 per cent reduced ventricular function as evidenced by decreasing cardiac output and a rise in atrial pressure. The value of the use of contractile force measurements has been in question since so many variables influence ventricular function. Among these are variations in heart rate, changes in ventricular volume, variation in ejection pressure during the interval of systole, changes in systemic venous pressure, and changes in systemic peripheral resistance. The extent to which each of these factors is operative in the assessment of myocardial contractile force has not yet been clarified. In the intact dog, Etsten & Li (61) determined the effects of diethyl ether and cyclopropane on ventricular function curves. Both left and right ventricular stroke work were augmented by light ether and diminished during deep ether anesthesia. Deep cyclopropane anesthesia produced no significant effect on left ventricular stroke work at a given end-diastolic pressure. These observations support earlier findings by Price et al. in man (59) in which cyclopropane increased right ventricular stroke volume, stroke work, and end-diastolic pressure. In dogs anesthetized with halothane, Shimosato & Etsten (62) showed that concentrations greater than 0.5 per cent decreased the slope of both right and left ventricular function curves, reduced left ventricular stroke power, and decreased the mean rate of ejection at any given end-diastolic pressure. These findings again are consonant with previous evidence to the effect that cyclopropane and ether, to a lesser extent, cause increases in catecholamine secretion whilst halothane is devoid of this property. Such observations also explain the depressant effect of all three agents on the heart-lung preparation of the dog.

Anesthetics and Circulation in Specific Vascular Beds

Cerebral circulation.—Wollman et al. studied the effects of anesthetics on the cerebral circulation and metabolism (63). After induction of an-

esthesia with thiopental, six healthy volunteers breathed 70 per cent nitrous oxide in oxygen, and were given *d*-tubocurarine intravenously. Since the plasma concentration of thiopental was low and *d*-tubocurarine probably does not affect cerebral blood flow or metabolism, the changes observed were largely owing to nitrous oxide. With arterial Pco_2 normal and cerebral blood flow therefore at a normal level, cerebral oxygen consumption decreased by 23 per cent. About one third of this change could be attributed to a slight decline in body temperature. When arterial Pco_2 was brought to 18.3 mm Hg by means of pulmonary hyperventilation, the mean jugular Po_2 decreased to 19.8 mm Hg—a level generally associated with suboptimal cerebral oxygenation. However, cerebral metabolic rate did not decrease further at this low level of Pco_2.

Anesthetics and venous circulation.—Lurie (64) reviewed this subject extensively. As in the case of myocardial function, the effects of anesthetics are obscured by a multiplicity of direct and indirect factors and there are few good studies of the effect of anesthetics on the venous circulation. Peripheral venous dilatation may be said to exist when there is a reduction in tone without elevation in transmural pressure. In general, during anesthesia the immediate effect is one of dilatation of venules and postarteriolar or capacitance vessels. With administration of thiopental there is increased distensibility and a fall in venous pressure. As a manifestation of this there is a decline in cardiac output, and a reduction in central blood volume. Venous pooling is marked by a tendency for the plasma volume to increase. During cyclopropane anesthesia, venoconstrictor activity is enhanced, the central venous pressure elevated and plasma volume tends to be reduced. The peripheral venous dilatation observed during induction of anesthesia with cyclopropane is, however, not consistent with the overall constrictor effect (65). This may be explained by the fact that sleep or loss of consciousness is associated with increased venous distensibility. During halothane anesthesia, peripheral vasodilation is observed as a decrease in resistance in muscular vessels. The increase in forearm blood flow during halothane anesthesia, as measured by Black (66), is due to a decrease in vascular resistance, probably the result of reduced vasoconstrictor tone as well as modification by halothane of the constrictor effect of norepinephrine on peripheral vascular smooth muscle.

Renal circulation.—Papper & Papper (67) reviewed the effects of preanesthetic, anesthetic, and postoperative drugs on renal function. Studies in the past consisted for the most part of measurement of the rate of urine formation and urinary composition, with little attention paid to glomerular filtration, tubular secretion and absorption, or renal blood flow. Thus an apparent antidiuretic hormone effect may not always be attributable to hormone secretion per se, and a particular response is dependent upon conditions of diuresis and solute load. Many clinical studies have been complicated by preoperative anxiety, dehydration, the effects of operation, and coexisting abnormalities of sodium or potassium balance. Furthermore.

a species difference may be marked as shown by differences in response to morphine in the rat, dog, or man. In man as well as laboratory animals pain or extrarenal alterations in hemodynamics such as decrease in cardiac output or increase in venous pressure have played a role in the total anesthetic effect. Despite these reservations, general anesthetics seem to have certain actions in common leading to a decrease in renal blood flow, decrease in filtration rate, and decrease in excretion of water and electrolytes.

Microcirculation.—Baez & Orkin (68) studied further the response of the microcirculation to anesthetics and circulating catecholamines. The omental and mesoappendix preparations of the dog were employed in the presence of anesthetics to measure the response to epinephrine, the caliber of arterioles and venules, capillary venous outflow, and rate of recovery. During light planes of anesthesia there was an overall enhancement of activity with diethyl ether, with cyclopropane and, perhaps surprisingly, with halothane. The latter defies explanation in view of the previously demonstrated relative inactivity of halothane in stimulating the sympathetic nervous system and its antagonism of the effects of catecholamines at the peripheral level. Methoxyflurane from the outset proved to be depressant to the microcirculation.

Anesthetics and myocardial irritability.—Dresel and his co-workers (69) carried out a series of experiments in this field with particular attention to cyclopropane. It will be recalled that Oliver & Shafer at the turn of the century had first demonstrated the lethal effects of adrenal extracts injected into animals in the presence of chloroform. Levy established the classic experiment of production of hydrocarbon-epinephrine arrhythmias in the cat, and Seevers et al. later applied this method to the study of cyclopropane. Price suggested that the spontaneous arrhythmias observed during cyclopropane anesthesia in man were due to the same mechanism. Dresel, Hart & Strömblad (70) pointed out that there were few qualitative differences between epinephrine-induced arrhythmias in hydrocarbon sensitized and nonsensitized preparations, but that quantitative differences were great. In nonsensitized animals a greater amount of epinephrine is required, the predominant rhythm is monofocal ventricular tachycardia and multifocal rhythm is unusual; ventricular fibrillation is even more uncommon. The pattern in sensitized animals varies with the dose. Bigeminal rhythm is observed with minimal doses of epinephrine in the dog sensitized with cyclopropane, following induction with thiopental. A small increase in dose of epinephrine, however, produces multifocal tachycardia or ventricular fibrillation. Small doses of atropine or vagal section protect the sensitized animal. Nonfatal arrhythmias in sensitized preparations are dependent upon the level of blood pressure; in the absence of sensitization, increase in blood pressure is necessary only insofar as a reflex increase in vagal activity depresses the sinus pacemaker or atrioventricular node to permit dominance of a ventricular pacemaker.

Dresel's studies were concerned further with bigeminal rhythm. In the

dog in which anesthesia has been induced with thiopental followed by cyclopropane, the vagi severed and arterial Po_2 and Pco_2 maintained at normal levels, small doses of epinephrine produced bigeminal rhythm. Dresel concluded that this was not due to a focus of increased ventricular automaticity firing at a greater rate, because the compensatory pause following the abnormal complex was of a duration sufficient to allow another such automatic beat to occur. A parasystolic focus was excluded by production of a sudden change in atrial rate which affected the duration of the compensatory pause without affecting the coupling interval. Bigeminal rhythm could be abolished by lowering the blood pressure, while increase in blood pressure changed bigeminal rhythm to a multifocal rhythm indistinguishable from the multifocal rhythm caused by an increased dose of epinephrine. Multifocal rhythm was not converted to ventricular fibrillation by extreme elevation in pressure. These observations suggest a clear difference between fatal and nonfatal arrhythmias in terms of effect of blood pressure.

Although stimulation of the severed distal end of the vagus produces arrhythmias in the presence of sympathetic amines (Robert's amine threshold test), such stimulation during cyclopropane anesthesia converted nonfatal arrhythmias to normal sinus rhythm (70). This was not the result of production of hypotension and there was no effect of vagal stimulation on the minimum dose of epinephrine necessary to cause ventricular fibrillation —another indication that ventricular fibrillation may result from a different mechanism. Moreover, the effect of vagal activity on nonfatal arrhythmias could be graded, perhaps involving a change in refractoriness or conductance in the atrioventricular node. Maintenance of a constant atrial rate decreased the effectiveness of vagal stimulation in converting arrhythmias to sinus rhythm. Multifocal ventricular rhythm was changed to bigeminal rhythm in animals in which sinus rhythm was not achieved. Finally, when bigeminal rhythm could not be converted to sinus rhythm there was an increase in the coupling rate. This profound effect of vagal stimulation on nonfatal arrhythmias suggests their origin in the atrioventricular node or bundle of His. This conclusion is supported by results of the intracoronary injection of acetylcholine into the left circumflex branch which reaches the atrioventricular node. Injection of acetylcholine into the left circumflex vessel during sinus rhythm caused atrioventricular nodal block, and epinephrine-induced arrhythmias were converted to normal sinus rhythm for a brief period. Neither effect was seen upon injection into the anterior descending branch.

Most investigators have employed thiopental to induce anesthesia in animals subsequently maintained with cyclopropane, but thiopental exerts a considerable effect on cyclopropane-epinephrine-induced arrhythmias. Thiopental lowers the dose of epinephrine required to produce bigeminal rhythm and multifocal rhythm is seen in higher incidence. Such potentiation, however, is not a property of all the barbiturates. MacCannell & Dresel (71) could not potentiate the arrhythmias with pentobarbital or amobar-

bital, although North & Price (72) found otherwise. The site of action of thiopental was again localized to the distribution of the left circumflex coronary artery.

Katz (73) produced evidence in the cat to suggest that cyclopropane-catecholamine arrythmias are blocked by a specific β-adrenergic blockade and that myocardial ectopic excitation may be attributable to β-adrenergic receptors. Cardiac arrhythmias were produced by injection of epinephrine, norepinephrine, ethylnorepinephrine, or isoproterenol during the inhalation of 25 per cent cyclopropane in oxygen. Injection of dibenamine, an α-adrenergic blocking agent, produced epinephrine reversal, decreased the pressor response to norepinephrine, and decreased the depressor response to isoproterenol. However, dibenamine did not consistently increase the threshold doses of catecholamines required to produce cardiac arrhythmias. In those instances where the arrhythmia-threshold doses of the catecholamines were increased, usually to twice control values, the result was often attributable to a modification by dibenamine of the pressor effect of the catecholamines. A β-adrenergic blocking agent, pronethalol, produced ethylnorepinephrine reversal, increased the pressor response to epinephrine, and markedly reduced or abolished the depressor response to isoproterenol. Arrhythmia-threshold doses of the catecholamines were increased to eight times those of the controls. Large doses of isoproterenol produced-β-adrenergic blockade and increased the arrhythmia-threshold doses of the catecholamines to four times those of controls.

Anesthetics and Respiration

Despite many questions raised in a review article by Dripps & Severinghaus many years ago (74), few new data have accumulated on the effects of anesthetics on the respiratory process. Perhaps it is the general lack of effect of anesthetics on the lungs that has caused so little work to be done. For the most part investigations have been directed toward the influence of anesthetics on bronchomotor tone and pulmonary reflexes and upon uptake by the lung of anesthetic gases, or to the effect of intermittent positive pressure breathing on thoracic and pulmonary dynamics—artificial respiration being such a common practice in anesthesia today.

Ngai, Farhie & Brody (75) studied the effects of trichloroethylene, halopropane, and methoxyflurane on central respiratory regulatory mechanisms. In midcollicular decerebrated cats, trichloroethylene in 1 to 2 per cent concentration, halopropane 1 to 2 per cent, and methoxyflurane 0.5 to 1.0 per cent depressed ventilatory responses to inhalation of carbon dioxide. These agents also elevated the electrical stimulus threshold of the medullary inspiratory center but did not change the magnitude of the maximal inspiratory response. One per cent trichloroethylene increased respiratory rate but decreased amplitude; tachypnea still occurred after vagotomy and carotid denervation. In contrast to earlier work on diethyl ether, the tachypnea was not clearly related to acidosis. The changes were similar with

halopropane but not as marked; the tachypnea could not be correlated with the degree of acidosis or hypotension, or prevented by carotid denervation or vagotomy. Methoxyflurane consistently decreased respiratory rate and amplitude. Thus, although these agents are all respiratory depressants, the mechanisms differ in several instances.

NEUROPHYSIOLOGY

Several aspects of this subject were discussed in the section on theories of anesthesia. Anesthetics may produce muscular relaxation through depressant effects on specific areas in the central nervous system, or spontaneous activity as well as reflex responses can be made to diminish and eventually to disappear. Recent work (76, 77) has provided electrophysiologic evidence of synaptic blockade at the spinal cord level by pentobarbital, thiopental, urethane, and diethyl ether. Ether has been shown to interfere with neuromuscular transmission. Ngai, Hanks & Farhie (78) examined the effects of diethyl ether, nitrous oxide, cyclopropane, and methoxyflurane on neuromuscular transmission and somatic reflexes in midcollicular decerebrate and spinal cats respectively. Diethyl ether was the only agent that significantly decreased the tibialis twitch response to indirect stimulation, but at an inspired concentration much higher than that required to produce areflexia. Cyclopropane and to a lesser extent nitrous oxide increased the twitch response. At least in the case of cyclopropane this was a postsynaptic response distinct from the depressant action on the central nervous system. All potent anesthetics tested, with the exception of methoxyflurane, abolished spinal (polysynaptic) and cephalic reflexes simultaneously. Methoxyflurane depressed the spinal reflex earlier and at a lower inspired concentration.

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