New Approach to Analgesia and Anesthesia

Anesthesia by Diffusion through Silicone Rubber

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Arteriovenous shunts of silicone rubber are used for administration of volatile anesthetics to experimental animals by diffusion of these agents through the silicone rubber into the blood. Clotting is prevented by coating the tubing with a heparin-silicone layer. The maximum depth of anesthesia is determined by selection of tubing of the appropriate length and thickness. Level of anesthesia is adjusted by adjusting the area of tubing exposed to the anesthetic liquid. Methoxyflurane produces deep anesthesia without a rebreathing system or production of hemolysis. Ether and halothane require a rebreathing system for deep anesthesia, and there is slight hemolysis at deep levels of anesthesia. With the appropriate shunt, long-term analgesia can be produced with methoxyflurane in awake dogs.

Several possible uses of this principle for the fields of research and clinical anesthesia are discussed.

We have reported that anesthesia can be produced in animals by diffusion of anesthetic gases and vapors through silicone rubber.[1] We demonstrated this by passing nitrous oxide, cyclopropane, ether or halothane (Fluothane) vapor over a small coil of silicone rubber tubing which was shunting blood from femoral artery to femoral vein. In those experiments, direct application of liquid ether or halothane was not feasible because of the production of severe hemolysis. Recently, however, we have found that methoxyflurane will not cause hemolysis when the liquid *is* applied directly to the silicone rubber tubing.[2, 3] In the present study we demonstrate that other volatile anesthetics in liquid form can be applied to Silastic shunts with little or no hemolysis, provided the tubing wall is of the correct *thickness*. It is the purpose of this paper, therefore, to demonstrate the feasibility of production of both analgesia and anesthesia in the dog via diffusion of anesthetic agents through silicone rubber.

Methods and Materials

Shunts

A small shunt was made from an 18-inch length of Silastic tubing 0.104 I.D. × 0.192 O.D.,§ which is enclosed in a sleeve of glass tubing 11 mm. O.D. (fig. 1). A large shunt is made from a coil of Silastic tubing 0.104 × 0.192 × 38 inches, placed within a 150 ml. beaker (fig. 2). A shunt of the same length was also made with thicker tubing, 0.125 × 0.250 inches.

Antithrombogenic Surface (Heparin or Protamine)

Systemic heparinization was used in most of these experiments because a dog's blood usually clots in Silastic shunts one or more hours after application of a volatile anesthetic. However, shunts tested for clinical use are coated with a thin heparin-silicone layer,[4] ¶ and systemic heparinization is thereby made unnecessary. We have also found that the shunts may be protected from clotting by coating them with a thin protamine-silicone layer. The layer is made by mixing 0.3 Gm. protamine sulfate powder with 14 Gm. ether and 2.5 Gm. Silastic adhesive,** stirred until

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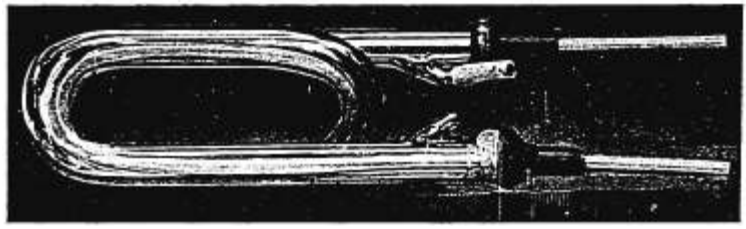

FIG. 1. Small shunt. The silicone tubing should be stretched before it is fitted at each open end of the glass sleeve. This will allow swelling without kinking. *A.* Arterial inflow; *B.* Port for inserting anesthetic liquid into external sleeve; *C.* venous outflow.

a thin, milky-white emulsion is produced. The mixture is centrifuged slowly for one minute to separate excess protamine crystals. The translucent milky supernate is then aspirated into the tubing to be coated, which is quickly drained dry. Excess ether is evaporated by suction for 1–2 hours and the tubing allowed to cure at room temperature for 12 hours before use. The thin white layer which lines the lumen reduces diffusion of anesthetic slightly but does not allow clot formation and has no effect on the dog's normal clotting time.

OPERATIVE PROCEDURE

Thirty dogs varying in weight from 8 to 34 kg. were used. Light anesthesia was induced with sodium thiamylal intravenously. The left femoral vein was cannulated for sampling of blood. One liter of saline was infused slowly into the left femoral vein throughout the experiment, which usually lasted eight hours. The left femoral artery was cannulated for sampling of arterial blood. The right femoral vessels were exposed, heparin (200 units /kg.) was injected and the shunt was inserted, using standard teflon connectors to cannulate the vessels. No atropine or other pre-medication was used. The dogs were allowed to awaken from the thiamylal, and when alert enough to whine and pull at their restraints, the outer surface of the shunt was covered with one of the volatile anesthetics. The dogs breathed spontaneously. No respirator or rebreathing system was used except where mentioned (fig. 3).

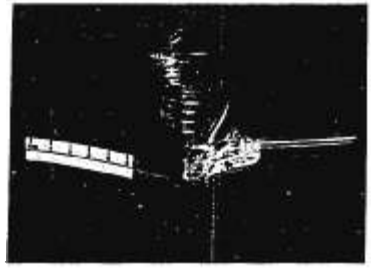

FIG. 2. Large (cup) shunt. The O.D. of the inner cylinder is 4.2 cm. and the I.D. of the beaker is 5.5 cm. This allows room for tubing swelling when liquid anesthetics are poured into the beaker. There are small perforations in the inner cylinder which allow drainage of the anesthetic liquid.

Results

METHOXYFLURANE

Small Shunt (0.104 × 0.192 × 18 inches). Dogs weighing 15 kg. or less were used. The shunt was inserted and the outer sleeve filled with 20 ml. methoxyflurane (Penthrane).†† This could be detected in the expired air by its odor within 5–8 minutes. There was an excitement stage during the first 15 minutes,

§ Extracorporeal and Medical Specialties Company, Inc., Mt. Laurel, N. J.

¶ Courtesy of Heyer-Schulte Co., Santa Barbara, California.

** Dow-Corning Medical Adhesive Type A, supplied by Extracorporeal and Medical Specialties, Inc., Mt. Laurel, N. J.

†† Courtesy, Dr. Norman C. Wheeler, Abbott Laboratories, North Chicago, Illinois.

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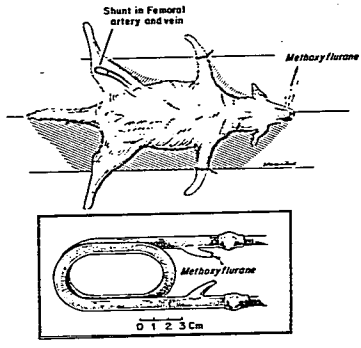

FIG. 3. Administration of methoxyflurane No vaporizer or rebreathing system is necessary.

with salivation, tachypnea, whining and pulling at restraints. The dogs then became quiet and hypalgesic. They glanced about but did not respond to pinprick. By 30–40 minutes deep surgical anesthesia had been reached. At this stage there was good relaxation and an endotracheal tube could be passed in a few dogs. The dogs breathed room air; no rebreathing system was necessary. Anesthesia was maintained for as long as eight hours by refilling the sleeve with methoxyflurane as necessary at hourly or two-hourly intervals. Because of swelling of the Silastic caused by exposure to methoxyflurane, the priming volume was decreased to approximately 5 ml., with each refilling. Lighter stages of anesthesia or prolonged analgesic states in awake dogs could be obtained by flushing some of the methoxyflurane out of the shunt sleeve with a mixture of 0.01 per cent methylene blue in saline. This aqueous mixture was not miscible with methoxyflurane, and the length of the blue column showed at a glance the amount of residual anesthetic in the shunt. When the methoxyflurane was removed completely by a saline flush, the dogs awoke in 20 to 40 minutes. The time to awakening was slightly shorter if the shunt was removed, indicating that some methoxyflurane still dissolved in the silicone rubber tube may have delayed the lowering of the blood concentration.

Large Shunt ($0.104 \times 0.192 \times 38$ inches). Dogs weighing up to 34 kg. were used. Methoxyflurane was added to the beaker to cover the Silastic coil completely. Induction of anesthesia was similar to that described for the smaller shunt. Surgical anesthesia was obtained in about 30 minutes. The dogs breathed spontaneously. An endotracheal tube was well tolerated, but no rebreathing system or reservoir bag was used in order to demonstrate that the surface area of the shunt was large enough for these large dogs to be maintained in surgical anesthesia despite the continued loss of anesthetic vapor in the expired air. The depth of anesthesia was regulated by changing the level of methoxyflurane in the glass beaker; this varied the area of Silastic exposed to the agent and the rate of entry of anesthetic diffusion into the blood. Anesthesia could be obtained in smaller dogs with use of less than the entire surface area of this shunt. For example, dogs from 15 to 20 kg. could be kept asleep by exposing only half the coil to the volatile anesthetic. For any given dog in which a rebreathing system with CO_2 absorption was used, the area of coil required for exposure to the liquid methoxyflurane to maintain anesthesia was much less than without a rebreathing system. With a rebreathing system the rate of loss of anesthetic was lessened and so decreased the area of silicone rubber necessary for a given level of anesthesia. In all these experiments the thickness of the tubing was held constant (0.104×0.192 inches) while the effective surface area was varied by changing the level of the liquid anesthetic. Obviously the tubing above the liquid level was also exposed to methoxyflurane vapor, but the vapor pressure of methoxyflurane (40 mm. Hg at 30° C.) is so low that the driving force for diffusion exerted by the vapor is relatively small compared with that of the pure liquid. Thus, the variation in the level of liquid anesthetic is the major determinant of the partial pressure and therefore of the number of milligrams of methoxyflurane which will enter the blood passing through the shunt. To illustrate the relationship of surface area, wall thickness and anesthetic depth, the following experiment was done.

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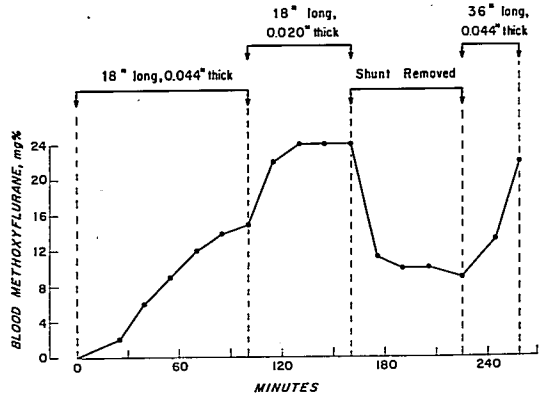

FIG. 4. Effect of tubing length and thickness on diffusion of methoxyflurane into the blood stream. Dog breathed spontaneously without vaporizer or rebreathing system and no attempt was made to control respirations. Respirations were shallow and slow during deep anesthesia and rapid during light anesthesia.

Effect of Surface Area and Thickness of Tubing on Depth of Anesthesia with Methoxyflurane. Dogs weighing 15 kg. were heparinized and allowed to breathe spontaneously without a rebreathing system. A small shunt (0.104 × 0.192 × 18 inches) was inserted between the femoral artery and vein. Blood flow through the shunt was 300–400 ml./minute. Methoxyflurane, 20 ml., was injected into the shunt sleeve after the dogs had awakened from the thiamylal. Samples for analysis of methoxyflurane were collected from the opposite femoral artery, put into oxalated tubes, and frozen immediately in dry ice and acetone. At the conclusion of the experiment the samples were mailed to Abbott Laboratories in dry-ice containers for analysis by gas chromatography.* The standard shunt was used for 100 minutes; then, the thickness of the tubing was decreased by approximately half by substituting tubing of 0.120 × 0.160 inches, but the length held constant at 18 inches. The shunt was then removed and the dog allowed to exhale methoxyflurane for one hour. Finally a shunt of the original wall thickness (0.104 × 0.192 inches) but twice the length (3.6 inches) was inserted. This approximately doubled the surface area, compared to the first shunt, while the thickness of the wall remained the same. These experiments demonstrated that doubling the tubing length or halving the wall increased the blood concentration of methoxyflurane almost twice the thickness. There was a corresponding increase in depth of anesthesia (fig. 4). There was no hemolysis at the end of this experiment.

Effect of Flow Rate on Production of Hemolysis by Methoxyflurane. In no experiment with methoxyflurane applied to shunts with normal blood flow was there *any* hemolysis, no matter how deep the anesthesia. However, if a shunt was soaked in methoxyflurane and temporarily clamped or almost completely occluded, slight hemolysis (40–60 mg./100 ml.) could be detected in a sample taken from the opposite femoral vein. Thus, diffusion of anesthetic from the Silastic into the blood continued even if the flow of blood through the shunt was slowed or stopped. Blood standing at the point of occlusion was exposed long enough to allow an accumulation of anesthetic sufficient to cause local hemolysis.

In order to determine the minimum flow rate through the shunt without production of hemolysis, the following experiment was done.

Fresh heparinized dog blood was passed through a standard small shunt (0.104 × 0.192 × 18 inches) at varying flow rates from 100 to 0 ml./minute by gravity and without re-

* Courtesy Dr. Norman Wheeler and Mr. Don Robinson, Abbott Laboratories, North Chicago, Illinois.

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cycling. Samples to detect hemolysis were collected during the middle of a run for each flow rate. No hemolysis was seen until the rate fell to 4 ml./minute, at which time there was a visible red tinge to the plasma. When the flow was stopped without removing the methoxyflurane, after two minutes there was gross hemolysis of the blood trapped in the shunt. In this *in-vitro* experiment the blood entering the shunt was free of methoxyflurane. Blood entering the shunt *in vivo* would contain a basal level of methoxyflurane so that hemolysis might be expected to appear at a flow rate a few milliliters higher than 4 ml./minute. Were these data to be extrapolated for clinical use, it should also be recalled that human blood is more resistant to hemolysis than dog blood. The implication for clinical use is that the shunt should not be constricted or occluded unless the anesthetic has been removed first.

Absence of Thrombophlebitis with Methoxyflurane. In three dogs a small standard shunt charged with methoxyflurane was inserted between the right femoral vessels and anesthesia was maintained for 6–8 hours. A similar shunt without methoxyflurane was inserted into the left femoral vessels. Both iliac and femoral veins were removed from the dogs eight days later. There was no gross or histologic evidence of thrombophlebitis either in the vein exposed to the high concentrations of methoxyflurane in the shunt effluent or in the control vein of the opposite leg (fig. 5).

Analgesia With Methoxyflurane in the Awake Dog. Dogs weighing 16 to 18 kg. were used. Under pentobarbital (Nembutal) anesthesia, a short loop of Silastic tubing was inserted between the proximal jugular vein and carotid artery and brought out through an incision on the dorsal surface of the neck. Only two inches of the tubing were exposed. The neck was wrapped with roller gauze so that the dogs could not chew at the tubing. Such tubes will stay open for about a week in dogs if no volatile anesthetic is applied. The dogs were allowed to awaken and were returned to their kennels. Two or three days later, while awake and erect, they were given heparin intravenously (200 units/kg.) The carotid-jugular tubing was transected and attached to a short shunt with glass sleeve ($0.104 \times 0.192 \times 18$ inches). No premedication was given. Methoxyflurane (20 ml.) was introduced into the outer sleeve of the shunt and the shunt secured to a collar worn by the dog. The dogs were allowed to walk about. After 15 minutes one dog had a brief period of tachypnea, the only evidence of an excitement stage. The others did not pass through an excitement stage. By 30 minutes all dogs appeared less alert and slightly drowsy. They remained in a sitting position. By 45 minutes they appeared to reach a plateau between hypalgesia and analgesia. Either they did not respond to deep pinprick or they responded only sluggishly. If not stimulated they would doze into a prone position with their jaws resting on the floor, but they would stand if stimulated by a loud noise or repeated deep painful stimuli. Dogs remained in this stage throughout the eight hours of each experiment as long as the shunt sleeve was refilled with methoxyflurane. They became alert and frisky an hour after removal of the shunt and responded quickly to deep pain. This demonstrated that analgesia could be obtained without surgical anesthesia if the shunt was small in relation to the weight of the animal, even if premedication was omitted. We have recently shown that a 6-inch carotid-jugular shunt, of which only one inch is exposed to methoxyflurane, will produce profound analgesia in awake dogs. However, analgesia does not appear until 24 hours after application of the liquid anesthetic, and only 1 ml. is necessary per day to maintain this analgesia.

Other Volatile Anesthetics

Diethyl Ether. Unlike methoxyflurane, stage III anesthesia could not be produced by diffusion of ether through silicone rubber unless a rebreathing system was used. The thickness of the shunt tubing which was satisfactory for methoxyflurane (no hemolysis) caused immediate hemolysis when liquid ether was applied. By increasing the thickness of the wall, the *rate* of diffusion of ether into the blood was reduced and hemolysis was avoided, except during very deep anesthesia. The original large-cup shunt was used, except that the tubing was $0.125 \times 0.250 \times 38$ inches,

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FIG. 5. Histologic section of iliac veins showing lack of thrombophlebitis eight days after exposure to shunts with and without methoxyflurane. *Left:* left iliac vein. Control shunt. No anesthetic. Blood flow for six hours. *Right:* right iliac vein. Shunt containing methoxyflurane. Blood flow for six hours.

i.e., 18 mils. thicker than the tubing used for methoxyflurane. Dogs weighing 12 to 22 kg. were used. The shunt was inserted into the right femoral vessels under light sodium thiamylal anesthesia; the dogs were allowed to awaken before ether was added. No premedication was given. Samples for detection of hemolysis were taken every 10 minutes from the left femoral vein.[9]

Seventy-five ml. of ether were added to the shunt cup. The liquid boiled because of the warm blood coursing through the tubing. Ether was noticed on the breath of all dogs by 5–6 minutes. Without a rebreathing system there was a prolonged excitement stage, with pulling at the restraining ropes, whining, salivation, breath-holding and tachypnea. After 40 minutes the smaller dogs became analgesic but remained awake and somewhat quiet; they never slept. The larger dogs continued in the excitement stage. There was no hemolysis up to this time. A small amount of sodium thiamylal (25 mg. in 1 ml. solution) was injected so that an endotracheal tube could be inserted. As the dogs began to awaken, the endotracheal tube was attached to a rebreathing system with a CO_2 absorber, and oxygen flowing into the reservoir bag. The dogs were allowed to breathe spontaneously. The smaller dogs reached stage III anesthesia after 15 minutes and became apneic in 30 minutes. Hemolysis appeared in stage III (50–60 mg. hemoglobin/100 ml. plasma) and increased by the time of onset of apnea (100–125 mg./100 ml.). The largest dogs reached stage III in about 30 minutes and were allowed to continue to apnea, which occurred about an hour from the beginning of insertion of the rebreathing system. Hemolysis appeared in stage III (70 mg./100 ml.) and increased slightly at the point of apnea (85 mg./100 ml.). At the point of apnea the ether shunt was removed and respiration was assisted manually for a few minutes until spontaneous breathing returned. The dogs were then allowed to breathe without the rebreathing system, and were awake in 30–50 minutes.

Halothane. A shunt of the same size (0.125 × 0.250 × 38 inches) was used, since halothane caused hemolysis when applied to tubing with a wall thinner than this. Again, deep anesthesia could not be produced unless a rebreathing system was used. With a rebreathing system, induction time to very deep stage III anesthesia was 15 to 20 minutes. There was no hemolysis during light anesthesia; during deep anesthesia maximum hemolysis was 65 mg./100 ml.

Swelling of Silastic Exposed to Volatile Anesthetics. In previous experiments we showed that anesthetic gases diffuse through silicone rubber without causing any swelling.[5, 6] However, all of the volatile anesthetics used in the present study caused the Silastic to

[9] Plasma hemoglobin method determined by the ortho-tolidine method of Lewis.

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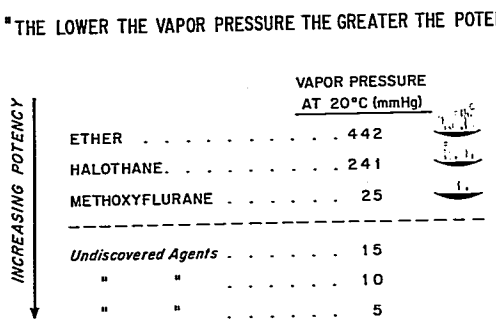

FIG. 6. Volatile anesthetics above the dotted line can be administered either through the pulmonary route or by diffusion through silicone rubber. However, one might predict that agents found below the line could be given only by silicone diffusion and and that they might also be optimal for chronic analgesia in awake patients with arteriovenous shunts.

swell within the glass sleeve or beaker. For example, when a Silastic tube 18 mm. long and 5 mm. O.D. was inserted in methoxyflurane, the tube increased in length to 23 mm. and in O.D. to 7 mm., by two hours. The tube returned to original size after all of the anesthetic had evaporated. For this reason the external sleeves of Silastic shunts are made extra large and the tubing is stretched before it is fixed by the gaskets at the exits of the glass sleeve (fig. 1); this allows for swelling without kinking.

Discussion

Interpretation of Results

It has been shown[7] that nonpolar or lipid-soluble compounds are more soluble in silicone rubber than the polar compounds. This may account for the high solubility of the volatile anesthetics in silicone rubber and their rapid diffusion through it. This newly-demonstrated property of silicone rubber allows the diffusion of volatile anesthetics directly into the blood stream. The rate of diffusion is inversely proportional to the thickness of the wall and directly related to the surface area of the tubing exposed to the anesthetic. When no rebreathing system is used, the maximum depth of anesthesia will depend upon the area of the shunt, the size of the dog, and the potency of the agent used. Methoxyflurane is so potent that any depth of anesthesia can be reached in a dog of any size without a rebreathing system as long as an appropriate length of tubing is exposed to anesthetic. On the other hand, the less potent agents, ether and halothane, require a rebrreathing system before deep anesthesia is achieved.

Vapor pressure probably plays a less significant role in diffusion of the anesthesia through silicone rubber because the tube is immersed in the purely liquid anesthetic. Ether and halothane have high vapor pressures (fig. 6) and might be removed from the lungs at a rate faster than either diffuses into blood. However, many factors are involved here, including the partial pressure of the anesthetic in the blood and the blood–gas solubility coefficient. Important too is the relationship between lipoid solubility and potency. Less of the highly lipoid-soluble methoxyflurane is required for anesthesia than halothane or ether, both with considerable but lesser solubilities.

These differences in physical properties may explain why hemolysis is not seen with methoxyflurane but appears during deep anesthesia with ether or halothane. Blood concentrations of these anesthetics are higher within the shunt than at any other place in the circulation. We do not know which of the three agents is more productive of hemolysis on a molar basis when added directly to blood, but if they are assumed equal, one would expect the least potent anesthetic to cause the most hemolysis, since higher blood levels are needed to produce sleep. The more potent agent, methoxyflurane, can induce sleep with a much lower blood concentration and thus does not

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approach the level for hemolysis. For example, in the dog whose data are shown in figure 4, the deepest anesthesia possible without apnea was produced by methoxyflurane at a blood level of 24 mg./100 ml. However, blood from that dog did not begin to show hemolysis until additional methoxyflurane was added to the blood in a test tube. There was a tinge of hemoglobin when the concentration of methoxyflurane reached 30 mg./100 ml. and obvious hemolysis at 41 mg./100 ml.

Although the blood entering the shunt mixes with a peak concentration of anesthetic, apparently there is quick dilution, because thrombophlebitis was not seen in the large veins exposed continuously to effluent blood from the shunt.

Swelling of the silicone rubber probably is due to the high solubility of the volatile anesthetics. Silicone rubber may be considered a gel, in which the polymeric units undergo segmental rotation and expand the polymer as it imbibes anesthetic liquid. Swelling ceases when saturation or equilibrium is reached.

The ability to produce prolonged analgesia without sleep is an intriguing feature of the silicone-diffusion principle. It demonstrates that precise and stable rates of administration of methoxyflurane can be achieved by selecting the appropriate size shunt. If one wishes to produce only analgesia, the shunt used is smaller than that necessary for surgical anesthesia.

Implications: The importance of this newly-demonstrated property of silicone rubber is *not* that it will substitute for any of the present methods of anesthesia used for operation, but rather that it may open up areas of investigation and fields of clinical usefulness not previously possible. We are presently exploring three of these areas:

a) *Prolonged Analgesia.* Cancer patients with intractable pain might have a chronically-implanted shunt with a surface area large enough for analgesia but not for anesthesia. This shunt would be worn on the wrist similar to that used for patients with renal failure who require chronic hemodialysis. It might provide a means for self-administered analgesia in awake patients. The analgesic properties of methoxyflurane in awake patients have been described lately.[8]

b) *A Means of Looking for a New Class of Potent Low-pressure Anesthetics.* It is generally held that potency increases with decreasing vapor pressure. If we arrange the volatile anesthetics according to potency [9] (fig. 6), then one would not expect to discover agents of practical value much more potent than methoxyflurane because such liquids probably would have even lower vapor pressures and would be difficult to vaporize. The dilemma in searching for inhalation agents of increasing potency is that there would be no way to administer them through the lungs to discover if they had anesthetic properties! But such liquids could easily be tested by diffusion into the blood through silicone rubber. Probably such compounds exist today on the shelves of pharmaceutical houses. These agents would be hydrocarbons with structures analogous to those of known volatile anesthetic, but with vapor pressures so low as to preclude any test by administration through the pulmonary route. For example, it would be interesting to determine the potency and efficiency of an agent with a vapor pressure of 5 or 10 mm. Hg. These low-vapor-pressure anesthetics would be optimal for silicone diffusion anesthesia because: a) their greater potency might allow one to obtain analgesia by applying only a few milliliters of the liquid to a short shunt; and b) analgesia would last a long time between applications because loss through the lungs would be minimal.

c) *A Means of Studying the "Non-anesthetic" Effects of Prolonged Exposure to Low Levels of Anesthetics.* It has been shown that nitrous oxide may produce remission in leukemia,[10] that other anesthetics may prevent mitosis of rapidly dividing cells,[11] and that anesthetics may also suppress immune reactions.[12] It is theoretically possible, therefore, that one day anesthetic gases or vapors might be allowed to diffuse through Silastic shunts worn by uremic patients in order to prevent rejection of transplanted tissues. A similar shunt could be worn by a patient with leukemia. An arterial-arterial shunt might allow the diffusion of anesthetics or other effective drugs into the circulation to a neo-

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plasm, in the manner in which chemotherapeutic agents are now infused.

Summary

Silicone rubber arteriovenous shunts are used for administering volatile anesthetics to experimental animals by the diffusion of these agents through the Silastic into the blood. The maximum possible anesthetic depth is related directly to tubing lengths and indirectly to wall thickness. Anesthetic depth is adjusted by varying the surface area of tubing which is exposed to the liquid anesthetic. Analgesia can be produced in awake dogs, with methoxyflurane and an appropriate shunt. Methoxyflurane is the optimal agent for silicone-diffusion anesthesia because of its high potency and low vapor pressure. Hemolysis is not seen with methoxyflurane. Increasing the wall thickness of the shunt prevents hemolysis when ether and halothane are used, except at deep levels of anesthesia.

The potential use of this new method for self-administered analgesia, for searching for high-potency, low-vapor-pressure anesthetics, and for studying the "non-anesthetic" properties of anesthetics, is discussed.

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