Anesthesiology
48:104–110, 1978

The Pressure Reversal of a Variety of Anesthetic Agents in Mice

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The aim of this work was to study in mammals the ability of high pressures to reverse the anesthesia produced by a wide range of general anesthetics. Dose–response curves were obtained using mice at pressures ranging from 1 to 125 atm for five agents, namely α-chloralose, ethylcarbamate, phenobarbital and, for comparison, nitrogen and argon. The increase of ED_{50} was found to be a linear function of pressure in each case, but the proportionate increases in ED_{50} with pressure were greater for the three non-inhalation agents than for the two gases. Thus, the ratio of ED_{50} at 100 atm to that at 1 atm was 1.74 for α-chloralose, 1.68 for ethylcarbamate, and 1.54 for phenobarbital. On the other hand, the corresponding ratios for argon and nitrogen were only 1.36 and 1.34. The potencies of three short-acting agents (trichloroethanol, ketamine, and alphadione) were shown to increase with decreasing pressure, although ED_{50} values could not be obtained. It is concluded that pressure reverses the actions of a wide variety of anesthetics in mice. The results of this study are not inconsistent with either the fluidized lipid membrane or the critical volume hypotheses of anesthetic action. (Key words: Theories of anesthesia, critical volume; Hyperbaria, reversal of anesthesia; Anesthetics, intravenous, ketamine; Anesthetics, intravenous, steroid, alphadione; Hypnotics, barbiturates, phenobarbital; Hypnotics, α-chloralose; Hypnotics, urethane.)

IN THE FIRST DEMONSTRATION of the pressure reversal of anesthesia, Johnson and Flager (1950) showed that anesthesia induced in tadpoles by ethanol and urethane was abolished by increasing the pressure.[1] Subsequent studies of inhalation agents in newts and mice have lent support to the concept that anesthetics act by expanding hydrophobic regions in the central nervous system (the critical volume hypothesis).[2–4] Few studies of intravenous agents in mammals have been reported, however, largely because the ambiguities that are imposed by pharmacokinetics restrict such studies to favorable cases[5] or to technically difficult procedures.[6] In this study, we examined the interactions between pressure and anesthetic potencies in mice of six intravenous agents, and, for comparison, two gaseous agents. We were able to demonstrate unequivocally pressure reversal even with moderately short-acting agents. In each case we confirmed our result by demonstrating that pressure reversal was reversible, as follows: after anesthesia had been reversed by applying pressure it was reimposed by lowering the pressure again, thus showing that the hyperbaric, rather than the temporal, vector was responsible for the reversal of anesthesia. Our data suggest that the concepts of the critical volume hypothesis may be applied to a wide range of general anesthetics acting in mammals.

Methods

Two types of pressure chamber were employed. A single 34-liter chamber was used for the longer-acting agents, whereas three 300-ml chambers allowed the more rapid changes in pressure required for the shorter-acting agents. The 34-liter chamber is constructed from a flanged cruciform cast-iron steam pipe with a 7-inch ID, fitted at each end with a window fashioned from 4-inch-thick plexiglass held in aluminium retainers sealed with "O" rings. This chamber accommodates two seven-compartment rotatable, cylindrical cages placed on carriages in front of the windows. Two mice, probed for rectal temperature, are placed in the center of the chamber. A muffin fan in the third arm and a heat exchange unit with fan in the fourth arm provide efficient gas mixing and heat distribution. Set temperature is maintained ± 0.1 degree C by circulating water through the internal heat exchanger and an outer jacket. The temperature is controlled by a thermistor in the chamber, which operates a valve allowing short pulses of either hot or cold water into the heat exchanger.

The smaller stainless steel chambers are those described earlier.[7] One is fitted with a thermistor, and they are heated by an external hot air blower. A temperature increase of 3 C resulted from a typical compression.

Pressure in the large chamber is monitored by one or more of three Heise‡ bourdon-tube gauges. Pressure in the smaller chamber is measured with a Marsh§ Master Test 200 gauge, measuring to 5,000 psi.

Metabolic gases were periodically checked by gas chromatography. They were controlled by soda lime in the small chambers and a soda lime–silica gel-activated charcoal (3:3:2) sandwich in the large chamber. Water is produced both by the soda lime and by

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Received from Harvard Medical School, Departments of Anaesthesia and Pharmacology, Massachusetts General Hospital, Boston, Massachusetts 02114. Accepted for publication July 20, 1977. Supported by a contract from the Office of Naval Research, Physiological Branch (Contract N00014-75-C-0727), with funds provided by the Naval Research and Development Command. K. W. Miller is supported by a Public Health Service Research Career Development Award (GM 00199) from the National Institute of General Medical Sciences.

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the mice, and we found that the silica gel controlled chamber humidity sufficiently to prevent the windows from fogging. It and the charcoal also controlled ammonia and other odors.

Response to anesthetics was measured as before.[7] The cages (or small chambers) were rotated at 4 revolutions/min and the ability of the mouse to remain upright observed in each of five complete revolutions (the rolling response). A score between zero and five could thus be obtained. Scores were recorded as percentages.

All experiments were carried out using male CD-1 mice (Charles River) weighing 20–30 g. Anesthetics were administered intraperitoneally. All doses were adjusted in proportion to body weight. Ethylcarbamate or urethane (Fisher), 2,2,2-trichloroethanol (Fisher), and ketamine hydrochloride (Ketalar, Parke Davis) were dissolved in physiologic saline solution before injection; α-chloralose (Aldrich) was dissolved in saline solution containing ethylene glycol, 40 per cent, before injection. Phenobarbital was supplied in solution (Invenex Pharmaceuticals) and diluted in saline solution. Alphadione (Althesin) was a gift of Dr. G. H. Philips (Glaxo, U.K.) and contained alphaxalone and alphadolone acetate (3:1) dissolved in saline solution containing 20 per cent polyoxyethylated caster oil.

After injection, the mice in their cages were sealed into the large chamber, which was flushed with oxygen for 5 min. The average time between injection and compression with helium was about 30 min. The rate of pressurization was kept at about 2 atm/min, and chamber temperature was maintained at about 35 C in order to maintain rectal temperature at 37 ± 1 C. The response of the animals was measured with increasing pressure and time until it was 100 per cent. Decompression was then begun, usually at about 1 atm/min, and the response measured as before.

For gaseous anesthetics the inert gas partial pressure was increased to the desired value after oxygen flushing was completed. Successive doses of gas could be added until a complete dose–response curve had been defined. The pressure was further increased with helium until pressure reversal occurred, and then another anesthetic dose–response curve was obtained. Compression rates were much slower (50 atm/hr) than with the other anesthetics because the same mice were also used later in experiments for observations of the effects of extremely high pressures (~200 atm), which will be reported elsewhere. The animals were thus partially pressurized late on the first day and the dose–response curves obtained the following morning.

With the shorter-acting anesthetics each mouse after injection was sealed in a small chamber, 0.5 atm oxygen added, the response measured, and the chamber then pressurized with helium. The time between final injection and pressurization could be as little as 3 min. Temperature regulation was observed to be less critical in the short exposures in these small chambers. No immediate change in response was elicited by rapid changes of temperature in the range 27–36 C. After compression (at about 8 atm/min) to the maximum pressure of the experiment, animals were observed until recovery of the rolling response occurred; then the pressure was rapidly decreased by as much as 60 per cent and the rolling response observed. In some experiments the pressure was increased and decreased several times. Controls showed no signs of decompression sickness[8] during such procedures.

Dose–response curves were analyzed on a digital calculator using the method of Waud[9] for quantal responses. The scale parameter (table 1) provides a measure of the slope of the dose–response curve.

All pressures are absolute unless specifically stated to be gauge.

TABLE 1. Variation of ED_{50} for Loss of Rolling Responses with Total Pressure

Agent	Total Pressure ATA	ED_{50} ± SE g/kg	Number of Animals	Scale Parameter* ± SE
Phenobarbital	1	.113 ± .0040	63	−12 ± 2.8
	2	.112 ± .0036	42	−14 ± 4.6
	50	.147 ± .0074	28	−15 ± 5.9
	75	.162 ± .0045	21	−23 ± 6.9
	100	.174 ± .0042	28	−24 ± 8.9
	75*	.15 ± .021	14	−7.6 ± 7.7
α-Chloralose	2	.0301 ± .00092	34	−13 ± 5.9
	10	.0314 ± .00095	70	−13 ± 3.1
	50	.0405 ± .00081	49	−21 ± 7.0
	25*	.0366 ± .00067	28	−27 ± 9.6
Ethyl carbamate	1	.97 ± .051	14	−17 ± 8.5
	2	1.01 ± .051	14	−19 ± 9.3
	40	1.32 ± .021	35	−55 ± 26
	70	1.45 ± .061	28	−24 ± 8.4
	52*	1.30 ± .055	24	−13 ± 6.5
Argon	19.1	18.1 ± .67 atm	35	−11 ± 4.6
	81	21.4 ± .78	17	−14 ± 8.7
	124	24.2 ± .59	14	−32 ± 16
Nitrogen	39.9	38.9 ± .94 atm	63	−12 ± 3.8
	81	45.7 ± .66	28	−32 ± 14
	121	48.8 ± .50	28	−46 ± 20

* Values obtained on decompression.

Results

Phenobarbital provided sleep times in excess of eight hours. Responses were measured only between three and six hours after injection. Analysis of the dose–response curves from a number of experiments

shows that ED_{50} increases with pressure (table 1). Furthermore, an ED_{50} of 0.16 ± 0.005 g/kg at 75 atm during compression compares well with one of 0.15 ± 0.02 g/kg later during decompression from 100 atm. In a few experiments we obtained a similar result on decompression to 50 atm. Thus, a response of eight of nine mice at 100 atm because zero of nine on lowering the pressure to 50 atm ($P \ll 0.005$).

Ethylcarbamate (1.2 g/kg) provided a sleep time of four hours. Dose–response curves were obtained at 1, 2, 40, and 70 atm. The ED_{50} increased with pressure from 1.0 g/kg at 1 atm to 1.45 g/kg at 70 atm (table 1), and the ED_{50} obtained on lowering the pressure was consistent with that obtained earlier during compression. In one experiment a response of nine of ten mice at 70 atm became four of ten at 52 atm ($P = 0.03$).

Sleep times with α-chloralose were little more than an hour, but induction took 30–60 minutes, so it was possible to load the large chamber and obtain complete dose–response curves at pressure. However, several additional problems were encountered with this agent. First, dose-dependent uncoordinated activity and twitching were a feature of α-chloralose anesthesia that appeared to be exacerbated by pressure. By way of contrast, the other agents tested gave good protection against the hyperexcitability normally encountered at pressure.[10] However, with α-chloralose above about 65 atm, extremely uncoordinated movements, and even mild clonic convulsions, prevented us from obtaining meaningful righting reflex data at still higher pressures. Consequently, all work was carried out at or below 50 atm. Second, rectal temperatures of animals injected with α-chloralose were extremely sensitive to environmental temperature, increasing, for example, 0.8–1.5 C during compression from 10 to 50 atm and then rapidly returning to their initial value. Furthermore, the observed response was unusually sensitive to rectal temperature. Consequently, rectal temperature was closely controlled in the range 36.7–37.2 C. Even so, an additional variable was found to be the presence of helium. Thus, at 1 atm oxygen plus 1 atm helium an ED_{50} of 30 mg/kg was determined, while in air in the chamber 70 per cent of animals righted at 36 mg/kg, even though the rectal temperature was slightly lower than usual. This effect of helium was not further investigated, but we carried out all measurements in the presence of at least 1 atm helium and included an extra determination at 10 atm. The ED_{50} values of phenobarbital and ethylcarbamate were found to be the same in 1 atm oxygen and 1 atm oxygen plus 1 atm helium (table 1). With these precautions, the dependence of ED_{50} on pressure was found to be essentially linear and of about the same magnitude as for phenobarbital and for ethylcarbamate (table 1). An ED_{50} obtained on decompression from 50 to 25 atm confirmed the reversibility of pressure reversal. A response of six of seven mice at 50 atm decreased to one of seven at 25 atm ($P = 0.002$) in one experiment.

Mice anesthetized with trichloroethanol had rather variable sleep times; nonetheless, marked and reversible effects of pressure were individually demonstrated. Thus, three mice received 311.4 mg/kg. The first awoke 40 min later at 136 atm. The pressure was decreased in 5 min to 54 atm, reanesthetizing the mouse for a further 5 min. The second awoke 30 min later at 116 atm and was reanesthetized for a further 30 min by lowering the pressure to 48 atm. The rolling response was again restored for a few minutes by increasing pressure to 116 atm, lost on decreasing pressure to 68 atm, and after 8 min restored to an average of 50 per cent by increasing pressure to 85 atm. The third mouse, after 27 min at 119 atm, had an average rolling response of 50 per cent, which was increased to 100 per cent at 129 atm and reduced to 20 per cent at 122 atm. A fourth mouse received 233.6 mg/kg and awoke after 6 min at 34 atm, was anesthetized again by lowering the pressure to 13 atm, and reawoke on increasing the pressure to 34 atm.

Alphadione (40 mg/kg) sleep times ranged from half an hour to an hour. Two mice were pressurized in small chambers to 130 atm. After recovery of rolling responses (21 and 25 min after injection), the pressure was decreased to 55 atm, completely restoring anesthesia. Rolling responses at this pressure were recovered in both cases 35 min after injection. Longer sleep times were produced by repeated injection. Six mice received injections of 100 mg/kg, with two to four subsequent doses of 50 mg/kg on awakening, and were then pressurized in small chambers to 90 atm. Rolling response was regained after periods ranging from 20 to 105 min. As before, pressure was decreased in each case at this point, yielding five mice with complete loss of rolling response (one at 62 atm and four at 35 atm). The sixth mouse had an average rolling response of 50 per cent at 35 atm. All animals recovered from anesthesia at the lower pressure within 60–165 min after the final injection.

The sleep time with ketamine, even after repeated injections, rarely exceeded 30 min. This made unequivocal demonstration of pressure reversal difficult. In three mice given 100 mg/kg the rolling response recovered at 68 atm after 15 to 30 min. Anesthesia was restored for more than 5 min by lowering the

pressure to 20 atm. A fourth mouse, which recovered the rolling response after 10 min at 68 atm, was reanesthetized for 5 min by decreasing pressure to 44 atm. All four animals regained normal behavior at pressure. In another case anesthesia was not restored by lowering pressure to 20 atm, which was the practical lower limit of pressure imposed by the oxygen levels.

Because of the uncertainties surrounding the results with ketamine and alphadione we confirmed them with experiments on 10–12-day-old rats, which have sleeping times of 2–4 hours in the large chamber. In one experiment a dozen 12-day-old rats were given 30 mg/kg ketamine intraperitoneally. Their response 55 min after injection was 50 per cent at 100 atm. They were decompressed at 12 atm/min to 50 atm; after 10 min their response was 0 per cent ($P = 0.007$). They were then recompressed at 12 atm/min to 100 atm, where they gave a response of 67 per cent. Similarly, with alphadione 40 mg/kg gave three and a half- to four-hour sleep times. Nine rats had responses of 67 per cent at 100 atm 85 min after injection, zero at 50 atm 98 min after injection ($P < 0.005$), and 100 per cent at 100 atm 104 min after injection. Nine other rats had responses of 72 per cent at 100 atm 90 min after injection, zero at 50 atm 104 min after injection ($P < 0.005$), and 55 per cent at 50 atm 164 min after injection.

One general observation from the quantitative studies was the tendency for the dose–response curves to become steeper with pressure (*i.e.*, the scale parameter[9] becomes more negative). This had been noted previously in the phenobarbital study.[5] Our data cover four more anesthetics. Regressing the 21 unweighted scale parameters in table 1 against pressure yields a slope of -0.45 ± 0.15, an intercept of -6.5 ± 10.1, and a correlation coefficient of 0.55. The F test concludes this slope to be less than zero with 99 per cent confidence. Thus, the population homogeneity of our sample of animals apparently increases with pressure. Intuitively, one would have expected pressurization to increase the scatter in our data because of the introduction of additional variables. One possible explanation is that the heat losses imposed by hyperbaric helium, together with our close control of environmental temperature, may actually have imposed a more uniform temperature on the group of mice.

Discussion

We were able to demonstrate pressure reversal with all the anesthetics we examined. This conclusion is supported by other studies, some of them only semiquantitative and carried out in tadpoles. Thus, our data for nitrogen and argon are broadly consistent with similar data of R.A. Smith, *et al.*,¶ obtained in mice, except in one particular. These investigators claim that the ED_{50} of these gases is not a linear function of pressure. We have analyzed their data and find that the curvilinearity is significant for nitrogen only (comparing a linear with a quadratic regression by analysis of variance, the F-test yields for argon $P > 0.05$ and for nitrogen $P < 0.01$). Our own less extensive data do not confirm this nonlinearity, nor does previous work with newts,[3] but more detailed work is needed to resolve this point. Our data for phenobarbital agree well with results of a previous study at 103 atm[5] by the same investigators. In addition, our study shows the ED_{50} to increase linearly and reversibly with pressure. Thus, our data for three anesthetics are in most respects in satisfactory agreement with independent work. Our quantitative data for α-chloralose and ethylcarbamate show relations between ED_{50} and pressure similar to that of phenobarbital. This is the first demonstration of pressure reversal with α-chloralose; an early qualitative study with tadpoles confirms our ethylcarbamate data.[1] Although α-chloralose pressure-reversed normally, it differed from the other anesthetics in not protecting against high-pressure excitability and in its sensitivity to low partial pressures of helium. Our work provides no explanation for these effects, but others have reported effects of helium at low partial pressures on the sympathetic nervous system and cardiovascular function.[11] Our demonstration of reversible pressure reversal of trichloroethanol, alphadione and ketamine in mice and young rats is new. The results are consistent with a decreased ketamine sleep time observed in guinea pigs at pressure[6] and the reversal of alphadione anesthesia in tadpoles.[12] More quantitative work than this in mammals will require determination of drug levels *in vivo*.

Our data extend to mammals the conclusion that the potencies of a wide range of anesthetic agents may be decreased by increased pressures.[12] Although these agents differ in many of their effects, it has often been supposed that they produce anesthesia by a common mechanism.[12–14] That these nonspecific agents are antagonized by a nonspecific agent such as pressure is appropriate, and is consistent with the above-mentioned view. Presumably, the anesthetic–

¶ Smith RA, Winter PM, Halsey MJ, et al: Helium pressure produces a non-linear antagonism of argon or nitrogen anesthesia in mice. Abstracts, American Society of Anesthesiologists, 1975, pp 217–218.

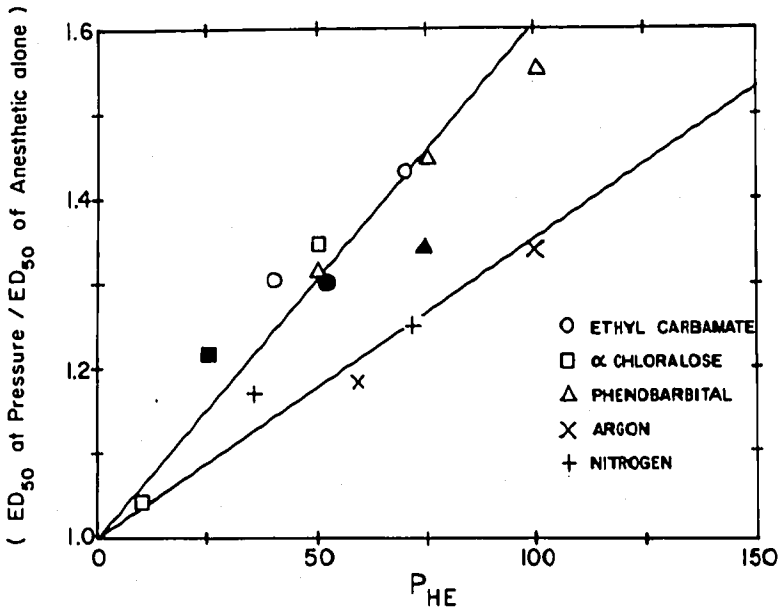

FIG. 1. Results for non-inhalation anesthetics plotted according to equation 4 and for gaseous anesthetics according to equation 5. The units of P_{He} are atmospheres. The lines were fitted by least-squares analysis through the origin. Since the standard deviations of the ED_{50}'s (table 1) vary considerably, each point was weighted by the reciprocal of the sum of the variances of the ED_{50} of the anesthetic alone and at pressure. The sum of the weights has been normalized to equal the number of data points. The slope (±standard deviation) for the non-gaseous agents is $6.1 \times 10^{-3} \pm 0.24 \times 10^{-3}$ and that for the two gases $3.5 \times 10^{-3} \pm 0.19 \times 10^{-3}$. The solid symbols represent ED_{50} values obtained during decompression.

pressure interaction must occur at several sites, not all of which are involved in anesthesia. In fact, pressure studies have distinguished one site where pressure reverses anesthesia from another where anesthetics reverse high pressure-induced convulsions,[15,16] but in general more detailed studies will be needed to resolve such questions. One such study shows that the nerve block occasioned by charged local anesthetics is not pressure-reversed, while that of the uncharged local anesthetics is.[17] This is consistent with the view that while the latter form acts nonspecifically, the charged form acts at a specific site and cannot be reversed by pressure.[18] In this case pressure provides a tool for distinguishing the two actions, as it may do in less well understood situations.[19]

Our results may be examined in the light of two current views of the mechanism of general anesthesia. These are the so-called critical volume hypothesis and the fluidized lipid hypothesis.

General anesthetics fluidize lipid bilayer membranes containing cholesterol, whereas lipid-soluble non-anesthetics (*e.g.*, tetradecanol) do not, and partial anesthetics (*e.g.*, tetrahydrocannabinol) do so to only a limited extent.[20–24] This effect is reversed by pressure.[20,21] Some of the agents we studied have already been reported to fluidize membranes.[22–24] In addition, α-chloralose, phenobarbital and trichloroethanol fluidize such lipid bilayers (Pang and Miller, unpublished observations). Thus, our data are self-consistent with the fluidized lipid hypothesis when cholesterol: phospholipid bilayers are used as a model of the site of action.

We may now use our quantitative data for intravenous anesthetics to test the critical volume hypothesis, which previous tests have confirmed for gaseous anesthetics in newts[3] and mice.[15] First, we extend the previous derivation for gases to non-inhalation agents, for which the fractional expansion may be written:

$$E_{50}^{1} = \frac{C_{50}^{1}\bar{V}_a}{V_m} \qquad (1)$$

where E_{50}^{1} is the fractional expansion of the anesthetic site of action at 1 atmosphere (superscript) when an ED_{50} concentration of anesthetic, C_{50}^{1}, is achieved. $\bar{V}_a$ is the partial molar volume of the anesthetic and V_m the molar volume of the site of action. The fractional expansion, E_{He}, caused by increasing the partial pressure of helium, P_{He}, is given by[3]:

$$E_{He} = \left(\frac{P_{He}x_{He}\bar{V}_{He}}{V_m}\right) - \beta P_{He} \qquad (2)$$

where x_{He} is the mole fraction solubility and $\bar{V}_{He}$ the partial molar volume of helium at the anesthetic site of compressibility β. For all simple solvents it is found that the compressibility term in equation 2 is larger than the expansion term due to helium dissolving, so net compression results. For more soluble gases (larger x), net expansion occurs. If C_{50}^{p} is the concentration at the anesthetic site required to produce an ED_{50} response at total pressure P_T, then according to the critical volume hypothesis:

$$E_{50}^{1} = \frac{C_{50}^{1}\bar{V}_a}{V_m} = \frac{C_{50}^{p}\bar{V}_a}{V_m} + E_{He} \qquad (3)$$

whence:

$$\frac{C^{p}_{50}}{C^{1}_{50}} = \left(\frac{\beta}{E^{1}_{50}} - \frac{\bar{V}_{He}x_{He}}{E^{1}_{50}V_{m}}\right)P_{He} + 1 = AP_{He} + 1 \quad (4)$$

Similarly, for gaseous anesthetics it has been shown that[3]:

$$\frac{P^{p}_{50}}{P^{1}_{50}} = A(P - P^{p}_{50}) + 1 = AP_{He} + 1 \quad (5)$$

where P^{1}_{50} is the ED_{50} partial pressure of the pure gas, P^{p}_{50} is the ED_{50} partial pressure in the presence of additional helium pressure, and P is the total pressure. If the sites and mechanisms of action of gaseous and non-gaseous anesthetics are identical, then linear plots of equations 4 and 5 should have equal slopes. Before such a test may be made, however, equation 4 needs to be modified to experimental variables by the assumption that the ratio of total doses per unit weight are an adequate representation of the ratio (C^{p}_{50}/C^{1}_{50}).

Figure 1 shows that the linear forms of equations 4 and 5 are supported by our data. Thus, our detailed results for three solid anesthetics are consistent with the critical volume hypothesis, just as previous detailed studies with gases have been shown to be.[3,15] However, the slopes for the gaseous and non-gaseous agents in figure 1 are unexpectedly found to differ by a factor of nearly 2. In tadpoles, on the other hand, our analysis of some preliminary data[12] suggests that halothane and alphadione pressure-reverse identically. Further quantitative work with tadpoles would be useful to resolve this point because of the simplicity of the pharmacokinetics. In the mouse we cannot rule out the possibility that pressure influences the pharmacodynamics of the intravenous agents, perhaps by changing the proportion bound to plasma protein. On the other hand, the membrane/buffer partition coefficient of pentobarbital is almost independent of pressure,[14] so that partial displacement of the barbiturate from a putative membrane site of action would not explain the greater pressure reversal observed. Nor would the non-ideal behavior of nitrogen and argon cause deviations of more than 10 per cent.[3] If, on the contrary, we do assume that the explanation for this slope difference is contained solely within equations (4 and 5), then we may distinguish two limiting cases. First, we may assume the two classes of agent act at the same site; it then follows that E_{50} must be smaller for the non-gaseous than for the gaseous agents. Second, we may assume different sites of action, with the non-gaseous agents' site showing lower solubility, x, and hence E_{50}, and/or greater compressibility, to yield the observed result. The correct interpretation may, of course, lie between these limits. More detailed experiments will clearly be necessary to settle these points, and to determine whether this slope anomaly is compatible with the critical volume hypothesis, or whether it has some artifactual explanation, as suggested by the data from tadpoles.[12]

Finally, our work also has a bearing on the problem of controlling the hyperexcitability observed in divers breathing helium–oxygen mixtures at great depths. Thus, the current use of nitrogen–helium–oxygen mixtures for divers[25] was suggested on the basis that protection against hyperexcitability could be obtained at pressure without incurring nitrogen narcosis because it would be pressure-reversed.[26] Our present results suggest that a wider variety of depressive agents may be employed for this purpose in a similar manner. Such an increase in the modalities available to treat this high-pressure neurologic syndrome could be an advantage in view of the limited effectiveness of gas mixtures at extreme depths.[26,27]

The authors thank Mr. Paul Wankowicz for help in constructing and maintaining the hyperbaric facility.

Note added in proof. A recent publication shows that the pressure reversal of alphadione also occurs more rapidly than that of gaseous anesthetics. Bailey CP, Green CJ, Halsey MJ, and Wardley-Smith B: J Appl Physiol 43: 183–188, 1977.

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