

Title : The Breeding of Mice Resistant to and Susceptible to Nitrous Oxide Anesthesia

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Anesthetic requirement varies slightly between animals of a given species. The reproducible nature of the requirement for a given animal suggests that the different values among animals do not simply represent the day by day variation of a homogeneous population. That is, a distribution of values exists about the mean anesthetic requirement which may permit a normal population to be sorted into two groups with reproducibly high or low anesthetic requirements. The present report documents this thesis for nitrous oxide ( $N_2O$ ). In addition, we find that by breeding males and females with the highest and with the lowest anesthetic requirements, these differences in anesthetic potency can be transferred to the offspring.

We examined the righting reflex in 500 male and 100 female CD-1 mice (25 to 30g) at  $N_2O$  concentrations of 1.29, 1.46, and 1.63 ata. Those mice which failed this test at 1.29 ata  $N_2O$  and above were placed into a LO group. Those mice which passed the righting reflex test at 1.63 ata  $N_2O$  and below were placed into a HI group. Each LO and HI animal then was retested 3 or 4 more times at weekly intervals. Only mice which consistently failed the righting reflex test at 1.29 ata  $N_2O$  were kept in the LO group, and only mice which consistently passed the righting reflex test at 1.63 ata  $N_2O$  were kept in the HI group. The resulting 4 males and 3 females in the LO group then were mated as were the 4 males and 5 females in the HI group.

We determined the  $N_2O$  ED<sub>50</sub> (the partial pressure of  $N_2O$  required to abolish the righting reflex in half the mice) in the 1st generation offspring. ED<sub>50</sub> measurements were performed in a hyperbaric chamber with the observer unaware of the identity of the animals. Chamber temperature was altered to maintain the rectal temperatures of two restrained mice between 36.5 and 38.0°C. The  $N_2O$  ED<sub>50</sub>s from the HI parent group were significantly higher ( $p < 0.005$ ) than those from the LO parent group (Table).

The males and females with the lowest and the highest anesthetic requirements in the 1st generation then were bred to give the 2nd generation. This process was repeated through 5 generations. Progressively greater ED<sub>50</sub> separations were obtained with each generation, such that the fifth generation animals were separated by approximately 0.5 atm in nitrous oxide requirement (Table).

These results may have both clinical and theoretical implications. The extremes achieved by breeding imply that variations in patient response may represent basic differences in resistance to anesthesia. They also imply that rare patients may be unusually susceptible to or resistant to anesthetic depression and that such tolerance or intolerance need not result from a pharmacological or physiological effect such as drug abuse or change in body temperature. Rather, the effect may be secondary to a genetically defined change in the central nervous system. If we can determine the alteration in structure that produces the altered anesthetic requirement, we may gain a clue as to how anesthetics act.

Table. Nitrous Oxide ED<sub>50</sub>s in Five Generations of Mice Bred for Their Resistance and Susceptibility to Anesthesia

Generation		HI	N <sub>HI</sub>	LO	N <sub>LO</sub>
		$N_2O$ ED <sub>50</sub> ±S.E. (ata)		$N_2O$ ED <sub>50</sub> ±S.E. (ata)	
1st	Males	1.59±0.025	22	1.51±0.040	8
	Females	1.72±0.028	22	1.54±0.043	11
2nd	Males	1.65±0.036	12	1.39±0.059	8
	Females	1.76±0.033	23	1.44±0.037	13
3rd	Males	1.69±0.036	26	1.41±0.034	17
	Females	1.78±0.036	20	1.36±0.026	13
4th	Males	1.71±0.036	19	1.35±0.020	23
	Females	1.80±0.058	15	1.36±0.025	26
5th	Males	1.74±0.087	10	1.29±0.013	21
	Females	1.86±0.024	22	1.32±0.016	32