Age and Ether Anesthesia in Mice.* (27106)

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The response of mice to ether anesthesia can be used as a measure of physiological aging. Diethyl ether is particularly suitable because it is not changed as it passes through the body, and the factors regulating intoxication and detoxification are relatively simple when compared with other anesthetics which are removed by the liver, the kidney, the intestine, or by other mechanisms. Streicher and Garbus(4) have shown age and sex differences in recovery time of rats from hexobarbital, and they explain these differences on the basis of sex hormone levels. But the major factors affecting rates of ether anesthesia—ether concentration in inhaled air, lung permeability, breathing rate, and heart output—have been shown to be dependent more upon age differences than upon sex differences. Thus age-related patterns of these variables will be reflected in the response of the animals to ether anesthesia. Sajner(3) studied ether consumption of juvenile and adult mice. He found that the younger the individual the relatively greater is the resistance to ether per unit weight. However, because in respiratory experiments in which the animal breathes a volatile drug the dose is unknown, and is determined by the animal, it is unreasonable to express the results as a function of weight.

Materials and methods. The subjects were 331 mice of the DBA/2 strain ranging in age from 2 weeks to 35 months, and never used previously for any experimental purpose. The following age groups were used, by months: 0.5, 1, 2, 5, 8, 14-18, and 20 and over; about 25 mice of each sex in each group. Each mouse was placed under a cylindrical jar (1500 ml capacity) on a perforated platform. The platform and the covering jar rested on a fiberboard washer placed on a ceramic hot plate. One ml of U.S.P. diethyl ether was sprayed, with a hypodermic syringe, through a hole in the fiberboard washer, onto the surface of the hot plate. The hot plate was kept at a temperature warm enough to vaporize the ether almost instantaneously, and the air temperature inside the jar ranged from 29-33°C. The apparatus is shown in Fig. 1. A stopwatch was started at the introduction of the ether and stopped when all body movements, except those of breathing, were seen to cease. Then the mouse was removed from the jar and laid on its back. Recovery time was recorded as the time between removal of the mouse from the jar to the time when the mouse first put all 4 feet on the ground.

FIG. 1. Apparatus used for anesthetizing mice.

Results. Behavior patterns. The mice from ages 1-8 months followed a similar behavior pattern. No visible reaction was shown immediately upon introduction of the ether. But soon the animal moved around the jar on its hind legs, leaning its front paws on the glass. At about 130 seconds it began to stumble, and went down on all fours. Then followed a circular movement on the belly, propelled by uncoordinated kicking; next a rocking motion, and defecation. After moving to the edge of the jar, the mouse turned over on its side, leaning its head against the glass. (In some mice the surface of the eye was brought into contact with the glass, but without any noticeable response.) The rear legs kicked, and the front paws stroked the nose vigorously. There was copious salivary

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secretion. The last movement was usually a twitch of the head or front paw. The eyes remained open.

On recovery, the first movement was usually a front paw twitch, followed by kicking. The animal moved in a circle, using the front feet and tail, swinging the tail rapidly in circles and thumping the floor. The front part of the body righted first, followed by the rear as much as 40 seconds later.

Very young mice (0.5 month) differed from the pattern described in that many of them reacted visibly to introduction of the ether and more often fell asleep belly down. One mouse was observed to vomit after recovery. Old mice followed the 1-8 month pattern, except for a tendency to fall asleep on their backs, rather than on their sides.

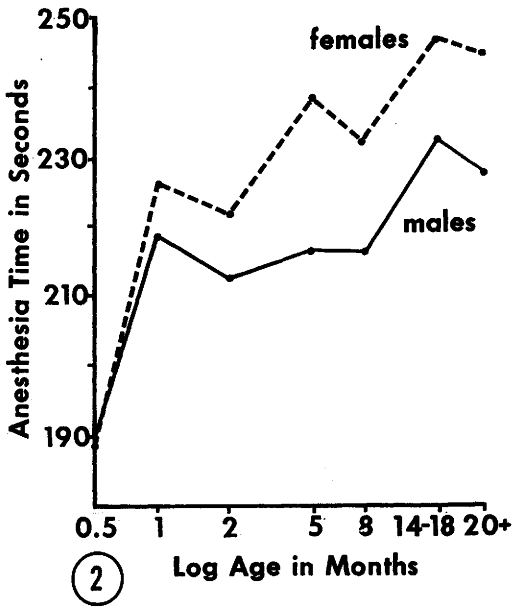
Time for anesthesia. Old mice resisted the ether longer than young mice, and females were more resistant than males. Fig. 2 shows the relation of age to anesthesia time. Differences among data for mice 0.5, 1-8, and 14-20+ months old were statistically significant ($p<0.005$) (Table I).

Time for recovery. Times for recovery are shown in Fig. 3. Old and young mice were alike in that they took a longer time to recover, but 2-8 month mice recovered rapidly. These differences were statistically significant for both males and females ($p<0.05$-0.01).

Ratio of anesthesia time/recovery time. Old and young mice were characterized by low ratios, 1-8 month mice by high ratios.

Variability of data. Old and young mice were found to be more variable than 1-8 month mice, both in recovery time and in anesthesia time (Table I). The differences among standard deviations of recovery times of 0.5, 1-8, and 14-20+ month animals were statistically significant ($p<0.05$-0.01). Recovery time was relatively more variable than anesthesia time. The standard deviations of anesthesia times for each age and sex group (Table I) averaged 20.7% of the anesthesia times, whereas standard deviations of recovery times averaged 50.3% of the recovery times. This difference in per cent was statistically significant ($p<0.001$).

Correlation between anesthesia time and recovery time. Anesthesia time and recovery time had a high correlation in adult mice ($r = 0.506$, $p<0.001$). But in very young and very old mice, they were uncorrelated. Differences in correlation coefficient between 0.5 month mice and 2 month mice were sig-



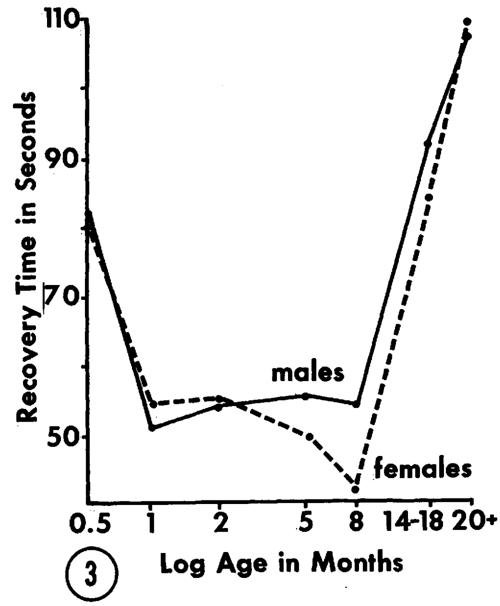


FIG. 2. Relation between age and ether anesthesia time for 140 male and 191 female mice. Points represent means for each age group.

FIG. 3. Relation between age and recovery time for the same groups as shown in Fig. 2.

TABLE I.

Age (mo)	Anesthesia time (sec.) ♂	♀	Recovery time (sec.) ♂	♀
.5	191.2 ± 73.7*	189.8 ± 56.2	82.5 ± 49.3	80.4 ± 54.8
1	218.7 ± 35.4	225.6 ± 56.0	51.4 ± 15.6	54.8 ± 20.6
2	212.8 ± 32.3	221.7 ± 40.4	53.8 ± 28.1	54.5 ± 21.1
5	216.1 ± 32.2	239.9 ± 67.0	57.4 ± 36.0	47.3 ± 23.8
8	216.8 ± 30.4	230.0 ± 48.9	53.6 ± 22.4	40.9 ± 18.0
14-18	231.2 ± 48.0	246.0 ± 36.2	92.7 ± 61.7	82.5 ± 40.2
20	226.0 ± 35.1	244.1 ± 45.0	107.2 ± 29.4	107.9 ± 81.3

* ± S.D.

nificant ($p<0.003$) and nearly significant between 2 month mice and 20 month mice ($p<0.06$).

Body weight and anesthesia susceptibility. No significant correlation was found between body weight and ether anesthesia time or recovery time among members of the same age group.

Discussion. Age differences in response to ether anesthesia parallel age differences in rate of breathing, heart rate(1), and diffusing capacity of the lung(2). More rapid breathing, more rapid heart rate, and higher diffusing capacity of the lungs produce faster intoxication in young mice than in the physiologically slower old mice. Females were over all slightly more resistant to ether (10% differences between the sexes); slower heart rate and breathing rate may be responsible.

The U-shaped curve for recovery time poses interesting questions. We would expect the old mice to recover slowly, as the same factors affect both anesthesia and recovery time. The relatively long time for the very young (0.5 month) mice to recover is probably due to the fact that once under anesthesia their breathing is extremely irregular and sometimes periodic. Before falling asleep the rate of breathing is rapid, but recovery time is probably prolonged because the respiratory center is more adversely affected than in older individuals.

The high variability of recovery times probably occurs because respiration, though regular during early stages of anesthesia, becomes irregular as it progresses to deep anesthesia. Once so disturbed, it continues irregular during recovery. Adult mice have less trouble with breathing under ether anesthesia, but juvenile and senile animals exhibit variable and individual patterns. The high correlation between anesthesia time and recovery time is expected in adults, since intoxication and detoxification mechanisms are similar. In very young and very old mice, however, extreme variability of physiological and behavioral patterns reduce this correlation to insignificance.

Summary. Mice of various ages were subjected to ether anesthesia in a chamber containing a fixed quantity of ether. Old mice took longer to fall asleep than did young mice. Old and young mice took much longer to recover than did adult mice of 1-8 months, and were more variable in response to ether, both behaviorally and physiologically. Sex was a factor of minor importance in time required to fall asleep, and made no measurable difference in time to recover. Time to fall asleep was correlated with time to recover in adults, but uncorrelated in young and old mice. Recovery time was more variable than time to fall asleep. Mechanisms to explain these results are discussed.

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