Sodium Pentobarbital Anesthesia and Mortality from X-Radiation in C_{57} Black Mice[1]

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While studying protective mechanisms against radiotoxicity in mice, it was noted that animals anesthetized during irradiation appeared to have a lower mortality than unanesthetized animals. This observation was further tested and verified, using 157 C_{57} Black mice between 255 and 502 days of age. Sixty-one animals (28 males and 33 females) were anesthetized with sodium pentobarbital, 10–15 min prior to irradiation. The anesthetic dose, administered intraperitoneally, was 0.05 mg/g body weight. The injected solution contained 10 mg sodium pentobarbital/ml. Eighty animals (40 males and 40 females) were given radiation without anesthesia. Sixteen animals (8 males and 8 females) were given 0.005 ml/g body weight of an 0.9% saline solution 10–15 min prior to irradiation. The anesthetized, unanesthetized, and saline-injected animals were approximately balanced as to age representation. Furthermore, we have been unable to demonstrate any significant age variation in response to irradiation in mice of this strain in this age range.

Mice were placed in thin cardboard boxes measuring $2.5 \times 8 \times 10.5$ cm, which were provided with cheesecloth screen air holes. Four animals were placed in each box, and 4 boxes (16 animals) were irradiated each time. The 4 boxes were placed so that they covered a rectangular area 16×21 cm, and this was, in turn, centered on a rice phantom which measured 47×47 cm and was 10 cm deep. This was similar to the radiation-scattering phantoms employed by Ellinger (*1*). The radiation used was produced by a 200 kv machine at 20 ma, with 0.5 mm Cu and 1 mm Al filtration. The target distance was 50 cm, and 36 r/min were delivered for a total air dose of 648 r. In our hands, these conditions of irradiation have repeatedly demonstrated that 648 r represents the $LD_{75/30}$ day dose for untreated mature mice of the C_{57} Black strain.

Only 16 animals could be irradiated at any one time. However, in almost every instance, one half the animals represented anesthetized or saline-injected animals, and the other half represented controls.

The results are shown in Table 1. Only 51% of the anesthetized animals died in the 30 days following irradiation, which is significantly lower than 75% of the unanesthetized animals which died (diff = 4.5 PE).

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The mechanisms by which sodium pentobarbital reduces radiotoxicity may be due to specific activity of the anesthetic agent or lowering of the metabolic rate and/or hypoxemia during anesthesia. Further work with animals receiving sodium pentobarbital or saline, either 1½ hr prior to or immediately after irradiation, suggests that alteration of a stress mechanism may be responsible for the observed results. Injections of saline, which probably act as "stressors," appear to increase the animals' susceptibility to radiotoxicity, whereas injections of sodium pentobarbital do not have this effect. The anesthetic seems to counteract the stress effect of its injection. Additional experiments of this type are in progress in the hope of obtaining more conclusive data on this point.

TABLE 1

EFFECT OF SODIUM PENTOBARBITAL ANESTHESIA* ON 30-DAY RADIATION MORTALITY IN C_{57} BLACK MICE

Treatment	No. animals	No. dying	Percentage dying
Control	80	60	75
Anesthetized*	61	31	51
Saline-injected*	16	14	87.5

* Anesthetic or saline was injected 10–15 min prior to exposure to radiation.

Studies which have correlated radiotoxicity with metabolic activity during or after irradiation indicate that increased metabolism may lead to increased susceptibility to the damaging effects of radiation and vice versa (*2–5*). Nembutal in anesthetic doses has been shown to lower oxygen consumption (*6*). Anoxia and hypoxemia have also been cited for their protective effects (*3, 4, 7–9*). Thus, reduction of radiotoxicity in anesthetized animals may simply be a reflection of impaired respiration during anesthesia. Actually, hypoxia and lowered metabolic rate may reflect one and the same protective mechanism.

Selye (*10*) mentions the findings of a number of workers which show striking similarities between the changes in animals following x-irradiation and those believed to accompany the "general adaptation syndrome." It has been suggested by Dougherty and White (*11*) that x-radiation has a direct and indirect effect on lymphocytes, the indirect effect being mediated through the pituitary and adrenal cortex. Although barbiturate anesthetics have been shown to act as "stressors" (*1⁰*), barbiturates have also been shown to prevent, under certain circumstances, the discharge of adrenal ascorbic acid following exposure to cold, and the hyperglycemia following various "stressors" (*12*). Thus sodium pentobarbital reduces the radiotoxicity of total body radiation probably through one or more of the proposed mechanisms.

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Polarizing Forces of the Muscarinic Moiety

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As an extension of some recent discussions (*1–6*) concerning the chemical constitutional characteristics of the muscarinic drugs, the following treatment dealing with a quantitative evaluation of the polarizing forces of moiety components has been found to be of particular value. Moreover, since it is a general type procedure which may well find application in other chemical constitution biologic activity problems, a brief communication of the basic approach is illustrated here.

The method of evaluation developed by Price (*7*) was applied in the estimation of the polarizing forces of the moiety components of the well-known muscarinic agents outlined in Table 1. Insofar as possible, the over-all intramolecular distances of the agents compared in each series are nearly constant. It will be seen that decreases in potency in each series are strongly correlated with the absolute difference in polarizing force of the component examined from that corresponding component in acetylcholine.

As is well recognized by other workers in this field, acetylcholine appears to be a "two-headed" moiety, although a quantitative expression of the character of the two heads has been lacking. Somewhat vague references to groups of "high" or "low" polarity and to the degree of methylation of the nitrogen do not

TABLE 1

	Polarizing force of bracketed function in dynes × 10^{-4}	Potency	
		Depressor	Gut stimulation
Series I			
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-\left[-O-\overset{O}{\overset{\|}{C}}-\right]-CH_3$	− 0.32	1	1
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-O-CH_2-]-CH_3$	− 1.21	1/3	1/10–1/20
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-CH_2-CH_2-]-CH_3$	+ 0.77	1/6	1/25–1/30
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-\left[-CH_2-\overset{O}{\overset{\|}{C}}-\right]-CH_3$	+ 0.89	1/70	1/50–1/100
Series II			
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-\left[-O-\overset{O}{\overset{\|}{C}}-\right]-CH_3$	− 0.32	1	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-I]$	− 0.39	≈ 1	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-Br]$	− 0.55	1/10–1/50	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-Cl]$	− 0.68	1/20–1/100	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-OH]$	− 1.46	1/200–1/1000	
Series III			
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}(CH_3)_3\right]$	+ 3.21	1	
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}H(CH_3)_2\right]$	+ 3.02	1/50	
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}H_2(CH_3)\right]$	+ 2.88	1/500	
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}H_3\right]$	+ 2.64	1/2000	