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Effects of Thiouracil and Sodium 5, 5-Diphenyl Hydantoinate (Dilantin Sodium) on Resistance to Lowered Barometric Pressures.*

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Attempts have been made recently to increase the resistance of animals to reduced barometric pressures by the administration of certain chemicals. Thiourea[1,2] and thiouracil[3,4] have been found to be effective in this respect.

Such drugs probably act by preventing the formation of thyroid hormone[5,6] thereby increasing the ability of the animal to tolerate the ill-effects of anoxia. It had been previously demonstrated that surgical thyroidectomy is beneficial[7,8,9] and treatment with thyroid or anterior pituitary substance harmful[7,8,10,11] to animals exposed to oxygen lack.

Another drug shown to protect rats and mice subjected to anoxia is dilantin.[12,13,14] Hoff and Yahn[14] have suggested the possibility that this drug operates by stimulating directly the activity of the nerve cells in the respiratory and cardiac centers.

It was considered important to compare the effects of thiouracil and dilantin and also to determine the action of the combination of these drugs on the resistance of rats to reduced barometric pressures.

Methods. Sixty-eight adult male rats weighing 190-250 g were employed. Half of these were fed a stock diet containing 0.2% thiouracil‡ for 3 weeks. Four groups of 17 animals were then established as follows: One group of the thiouracil-fed rats received intraperitoneal injections of 15 mg dilantin sodium‡ approximately 1½ hours before exposure to the reduced barometric pressures. Another group, consisting of controls fed ordinary stock diet, likewise received 15 mg injections of dilantin prior to exposure. The remaining 2 groups comprised thiouracil-fed rats given no additional treatment, and a series of untreated controls. Actually 2 experiments were conducted at 2 different times but because of the similarity in the results obtained, the data will be presented in pooled form.

All animals were subjected to a pressure of 148 mm Hg (39,000 feet) in a specially constructed low pressure chamber equipped with a neon light and several observation windows. The rats were brought to this pressure over a period of 20 minutes. Once the reduced pressure was established, the time for complete cessation of respiration in each animal was recorded. The pressure was maintained at 148 mm Hg for 2 hours. The remaining living animals were then brought to a pressure of 92 mm Hg (49,000 feet) over a period of 20 additional minutes.

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TABLE I.
Action of Thiouracil and Dilantin on Resistance to Low Barometric Pressures.

Treatment	Mean survival time (min.) ± standard error	Mean thyroid wt (mg) ± S.E.	Avg degree of lung hemorrhage %
Thiouracil	34.8 ± 6.0	73.3 ± 4.8	67.6
Dilantin	32.1 ± 4.2	17.0 ± 0.38	54.4
Thiouracil + Dilantin	>120*	60.0 ± 3.5	10.3
None	9.6 ± 1.0	16.8 ± 0.43	72.1

* 14 out of 17 rats in this group survived the 2-hour exposure to 148 mm Hg (39,000 feet). They succumbed when the pressure was lowered to 92 mm Hg (49,000 feet).

At the termination of the experiment all animals were autopsied, the thyroids and adrenals dissected, and weighed to the nearest milligram on a torsion balance. The eyes were examined for the development of lens cataract known to occur under conditions of anoxia[15] and the lungs for signs of hemorrhage. The lung condition was judged as 0, +, ++, +++, or ++++ depending on the severity of the damage, according to the description given by Lawson, Carnes, and Thienes.[16] The average degree of hemorrhage was computed by adding the number of "plusses" and dividing this total by the number of animals in the group. This figure was then multiplied by 25, giving the extent of hemorrhage as per cent.[16]

Results. The data presented in Table I confirm the previous findings[1,2,3,4,12,13,14] that thiouracil and dilantin are capable of increasing the resistance of rats to lowered barometric pressures. These drugs, in the dosages employed, appear to be equally active in producing this effect. It is also quite apparent that the combination of the 2 drugs is far more effective than either one alone.

The results indicate that the combination of drugs also affords considerable protection to the lung tissue. Whereas the greater majority of the untreated controls and those given only thiouracil display marked lung damage at autopsy, those thiouracil-fed rats which are given dilantin prior to exposure show either very little hemorrhage or none at all. A slight protective action also appears to have been exerted by dilantin itself. It does not seem likely that prevention of lung damage is directly accountable for the increased survival time since it has been found in both the present and in unpublished experiments that thiouracil or thiourea acting alone can considerably increase resistance to decompression without rendering any protection to the lung.

The marked increase in thyroid weight in animals receiving thiouracil has already been described at length.[17,18] This goitrous condition is associated with a state of functional hypothyroidism and, in the present experiments, was apparent in every rat given the drug in their diet. Adrenal weights, not included in Table I, were not significantly altered by any of the experimental treatments. Lens cataract which developed in a considerable number of animals subjected to decompression was not prevented by the drugs given singly or in combination.

The striking synergism between thiouracil and dilantin which probably act through different mechanisms to increase resistance to lowered pressures, is one of considerable interest and should be studied more intensively.

Summary. 1. Both dilantin and thiouracil prolong the survival time of rats subjected to reduced barometric pressures (148 mm Hg). 2. The combination is considerably more effective than either one acting alone. 3. The combination tends to reduce the extent of lung hemorrhage in rats subjected to decompression but has no effect on the development of lens cataract.

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