hormone, (d) re-entry of radioiodine into the blood stream in a protein bound form. How much of a role each one of the above factors might play in the ultimate derivation of the plasma curve requires further study.

While this work was in progress McConahey *et al.*[1] published the results of a similar study of serum radioactivity in hyper-, hypo-, and euthyroid individuals, after ingestion of I^{131}. They reported experiments on 31 patients divided as follows: 17 with hyperthyroidism, 9 euthyroid, and 6 myxedematous (one patient was studied twice, once while euthyroid and then after a "thyroidectomizing" dose of I^{131}). Their patients did not receive similar doses of radioiodine but rather there was a range from 0.1 to 100 millicuries of the drug. McConahey *et al.*[1] felt that there was little if any disturbing radiation effect on the plasma curves from the large doses given to some patients.

The principal finding of difference in McConahey's work from the work presented here, is the failure of our figures to differentiate hyperthyroid and euthyroid individuals. It seems reasonable to suppose that hyperthyroid individuals would show a different rate of increment and decrement of radioiodine in blood after an oral dose than would euthyroid individuals. The differences obtained here, however, were not sufficient to be used for diagnostic purposes and probit analysis of the data would not significantly separate the two groups in the time periods studied.

Summary. Curves of plasma radioactivity were determined for 25 patients after the ingestion of 100 microcuries of radioiodine. The patients were divided into 11 cases of myxedema, 5 cases of hyperthyroidism and 9 euthyroid individuals. The curves were constructed from plasma samples drawn at 30 minutes 1, 3, 6, 12, 24, and 48 hours. It was not possible to statistically separate, at these time intervals, the curves of the hyperthyroid and euthyroid individuals. The curves of the myxedematous patients, however, were significantly different from those of the non-myxedematous patients; thus the myxedematous curves show a later peak level, a lower peak level and a fall more delayed than do the curves of the non-myxedematous patients.

[1] McConahey, W. M., Keating, F. R., Jr., and Power, M. H., *J. Clin. Invest.*, 1949, **28**, 191.

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Acute Adaptation of Rats to Very Low Oxygen Pressure.* (17473)

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In a recent publication[1] the author reported evidence of depressed activity of the thyroid gland in anoxic rats. This thyroid depression may act as an adaptive change which would aid the accommodation to anoxia. Himwich[2] called attention to the evidence of Barach and others[3,4] which indicated that thyroidectomy increases the tolerance of rats to anoxia. Therefore, if anoxia were to result in a degree of functional thyroidectomy, this latter condition should increase the tolerance to more severe anoxia.

The experiments described here indicate that if normal rats are first exposed to anoxia for 2 or more hours at a low temperature, they can then withstand severe anoxia as readily as has been reported for surgically thyroidectomized rats.[3,4]

Method. The low pressure chambers were constructed from 9 liter vacuum desiccators.

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[1] Van Middlesworth, L., *Science*, 1949, **110**, 120.

[2] Himwich, H. E., personal communication, 1949.

[3] Barach, A. L., Eckman, M., Molomut, N., *Am. J. Med. Sci.*, 1941, **202**, 336.

[4] Streuli, H., *Biochem. Z.*, 1918, **87**, 359.

TABLE I.
Adaptation and Its Effect on Hours Survival at Low Air Pressure.

No. rats	Time at 268 mm Hg, 14°C,* hr	Time at 162 mm Hg, 14°C,* hr	Time at 162 mm Hg, 29-31°C, hr	Remarks
6 ♂	4	5		All lived
2 ♀	2	8		One died at end
3 ♂	4	2	3	All lived
7 ♀	2	1.5	4.5	Two died
		Controls		
5 ♂ and ♀		.12 ± .06		All died
1 ♀		1.0		Removed alive
17 ♂			.20 ± .18	All died
24 ♀			.25 ± .20	" "

* Temperature range 11° to 15°C.

They were continuously ventilated at the rate of 2 liters of air per rat per minute. The flow rate was measured at 760 mm Hg. The chambers could be operated either within a refrigerator or at room temperature. The experimental rats were Long-Evans strain, unfasted, male and female, old and young adults.

Results. Control rats were placed within the chambers at various temperatures (14-31°C) and the air pressure reduced within 3 minutes to 162 mm Hg. Within 6 to 15 minutes these rats developed convulsions and died. The "adaptation" experiments were conducted with the chambers placed within a refrigerator at 14°C (range 11° to 15°C) and the pressure reduced within 90 seconds to 268 mm Hg and maintained at that pressure for 2-4 hours. Then the pressure was further reduced to 162 mm Hg (14°C) and these conditions were maintained for 1.5-2 hours. At this point some of the chambers were removed to room temperature (29-31°C) and others were left within the refrigerator, the air pressure in both sets of chambers was still maintained at 162 mm Hg (oxygen pressure 32 mm Hg). After 4-6 additional hours under these conditions, 17 out of 20 rats remained alive and they were returned to sea level for further observation. These rats therefore endured for 5-8 hours anoxic conditions which killed 98% of controls in 10-15 minutes and this high degree of tolerance was developed in a 3-4 hour adaptation period.

The permanency of this adaptation was tested by the following experiment. Two rats were exposed to cold and anoxia as outlined in the above paragraph. The air atmosphere at 30°C was then replaced by 150 mm of pure oxygen, which is approximately equivalent to the sea level pressure of oxygen. After 4 hours the oxygen atmosphere was replaced by air at 162 mm and the animals succumbed in 12 and 15 minutes, essentially the same as unadjusted controls. Therefore, only 4 hours of oxygenation was adequate to destroy the tolerance which these rats had developed.

Of 20 rats adapted to anoxia as outlined above, only 3 died when exposed continuously to air at 162 mm for 5-8 *hours* (Table I). Of 46 *control* rats at the same pressure, 45 died in 4-27 *minutes* (0.06-0.45 hour) and one lived for one hour (Table I). Low environmental temperature was important in developing the tolerance of the adapted group, but the control rats died at a variety of temperatures.

The adapted animals were allowed to recover at sea level and room temperature. Their rectal temperature was 19-20°C if the entire exposure to cold and anoxia had been at 14°C. If the last 4-6 hours of anoxia was at room temperature, the rectal temperature was 1-2°C above room temperature (29-31°C). These animals were quite refractory to mechanical stimuli for the first 5-15 minutes following the anoxia period. However, within 2-3 hours, they would often eat and drink and within 24 hours they appeared normal. All of these animals were still alive one month after the experiment.

The eyes of the adapted animals showed striking changes. After 3 or more hours at an air pressure of 168 mm Hg the eyes were clouded by severe cataracts. Examinations of the lens directly by excision and indirectly by

the slit lamp† showed a well developed subcapsular cataract. Seventy percent (14 cases) of the severely anoxic rats developed cataracts during the period of anoxia but all of the cataractus lenses became clear within 60-120 minutes when the animals were allowed to recover at sea level.

Discussion. The acute adaptation to anoxia described here differs from the usual chronic acclimatization to high altitude. In the latter the subjects are said to live fairly normal lives (reviewed by Van Liere[5]) and the acclimatizing process requires weeks to develop[6] although it probably requires generations to become complete.[7] Furthermore, on return to sea level condition, the loss of true acclimatization is slow.[8] In our experiments the animals exhibited a very low level of existence but their tolerance to extreme anoxia developed within a few hours. On return to sea level oxygen pressure the adaptation was lost within a few hours or about as rapidly as it had developed.

This acute adjustment to severe anoxia may involve some or all of the following factors: (a) reduction of body temperature, (b) reduction of metabolic rate, (c) reduction of thyroid activity, (d) anaerobic metabolism. Evaluation of these possible factors must await additional experimental investigation.

It is possible that the adjustment to anoxia as illustrated in this report could have no significant relation to the thyroid gland, but in view of recent work[1] anoxic suppression of the thyroid appears to offer a plausible explanation for the acute adjustment to severe anoxia.

Britton and Kline[9] investigated the effect of temperature on survival of asphyxiated adult rats. Their results demonstrated that animals being asphyxiated in sealed chambers survived 2-3 times longer at 16-18°C than at a temperature of 31-32°C.

Previous investigators[10-12] have increased the tolerance of rats to anoxia by the administration of antithyroid drugs for 8 or more days preceding the low pressure exposure. In the experiments of Barach *et al.*[3] thyroidectomized rats were found to withstand 160 mm Hg for 2 hours (temperature not reported). However, Leblond[12] showed that such thyroidectomized rats must be well fed in order to withstand severe degrees of anoxia. The adapted animals described in the present work easily tolerated the severe anoxic conditions reported for hypothyroid or thyroidectomized rats.

Previous investigators[13,14] have observed cataracts from anoxia. The animals of Bellows and Nelson[13] were exposed to 225 mm until 50 percent of the rats were dead, after which 10% of those surviving had cataracts. Comparison of previous results with these reported here shows that in our experiments the anoxia was more severe, a greater number of rats survived the experiment, and more animals developed cataracts.

Conclusion. Rapid adaptation occurs in adult rats exposed to anoxia at low temperatures. This enables the animals to tolerate extreme anoxia (32 mm Hg pressure of O_2) at various temperatures (14-31°C) for a period more than 40 times longer than unadapted controls.

† These slit lamp observations were made by Dr. J. W. McKinney, Department of Ophthalmology, University of Tennessee College of Medicine.

5 Van Liere, E. J., Anoxia, its effect on the body, Univ. of Chicago Press, 1942, p. 140-156.

6 Houston, C. S., and Riley, R. L., *Am. J. Physiol.*, 1947, **149**, 565.

7 Monge, C., Acclimatization in the Andes, Johns Hopkins Press, 1948 (translated by D. F. Brown).

8 Norton, E. F., The Fight for Everest, London, 1925.

9 Britton, S. W., and Kline, R. F., *Am. J. Physiol.*, 1945, **145**, 190.

10 Gordon, A. S., Goldsmith, E. D., Charipper, H. A., *Science*, 1944, **99**, 104.

11 Hughes, A. M., and Astwood, E. B., *J. Aviat. Med.*, 1944, **15**, 152.

12 Leblond, C. P., PROC. SOC. EXP. BIOL. AND MED., 1944, **55**, 114.

13 Bellows, J., and Nelson, D., *Arch. Ophth.*, 1944, **31**, 250.

14 Biozzi, G., *Graefe's Arch.*, 1935, **133**, 423. (Eng. Abst. *Amer. J. Ophth.*, 1935, **18**, 692.

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