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THYROID STATUS OF DOGS CONTINUOUSLY EXPOSED TO ONE-HALF ATMOSPHERE

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FOREWORD

This report was prepared as part of the Laboratory Animal Medicine Residency, course No. OAY9936. The work was accomplished from June 1964 to July 1966, under task No. 775801 monitored by Colonel William P. Fife, Physiology Branch. The paper was submitted for publication on 1 September 1967.

The animals involved in this study were maintained in accordance with the "Guide for Laboratory Animal Facilities and Care" as published by the National Academy of Sciences—National Research Council.

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This report has been reviewed and is approved.



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ABSTRACT

Six male beagle dogs were maintained on ambient air at one-half atmosphere for 83 days and were monitored for protein-bound iodine (PBI), thyroid I^{131} avidity, plasma triiodothyronine uptake, and plasma 17-hydroxycorticosteroids. Data were compared with those from littermate controls held at ground level.

Increased I^{131} uptake and reduced triiodothyronine uptake were observed in the altitude-exposed dogs, while no change in the peripheral blood hydrocortisone level was seen. No difference in the gross, microscopic, or ultrastructural anatomy of the thyroid glands of groups was noted.

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I. INTRODUCTION

The exposure of man to low barometric pressures in high altitude flights led to considerable investigation into the effects of this environment on various organ systems and how the function of these systems could be modified to increase man's tolerance to hypoxia. Despite evidence of the influence of the thyroid gland on the utilization of oxygen by the tissues of the body, little has been done on the functional and anatomic changes occurring in this organ at altitude.

Some investigators (2, 3, 12) found that thyroidectomized rats survived longer at reduced atmospheric pressures than did normal controls. The increased altitude tolerance of thyroidectomized rats led others (7, 12) to consider antithyroid compounds as a method of increasing altitude tolerance. The effect of thyroid and antithyroid compounds appears to vary with the species. Low doses of thyroxine increase altitude survival time in mice but decrease it in rats. Thiouracil produces a greater increase in the survival time of rats than in that of mice. It has been postulated that these disparities occur because rats secrete more than optimal amounts of thyroxine, while mice secrete less (28).

Gordon and his associates (8) were among the first to report that exposure to low barometric pressures might induce changes in the structure of the thyroid gland. They noted decreased thyroid weight, lowering of the epithelium, and increased colloid in rats exposed for 6 to 8 days to pressures of 250 to 280 mm. Hg for 18 to 20 hours per day. The findings of Timiras et al. (22) were somewhat different. They moved experimental rats from a laboratory at sea level to a facility 12,000 feet

above sea level and observed that significant enlargement of the thyroid, adrenal, and pituitary glands occurred after 2 months. The offspring of these rats, however, were no different from those of controls maintained at sea level.

The thyroid avidity for I^{131} and the plasma protein-bound iodide (PBI) have been shown to be modified by hypoxia. Van Middlesworth (23) showed that the thyroid uptake of I^{131} and the PBI were considerably less in the altitude-exposed animals than in the controls. Under similar conditions, DeBias and Wang Yen (4) found an increase in I^{131} uptake by the thyroid, and increased erythrocyte triiodothyronine (T3) uptake in rats exposed for 24 hours to a simulated altitude of 25,000 feet. An indication that altitude-induced changes in thyroid function might be temporary came from the work of Verzar and his associates (24) in Switzerland.

The effects of altitude on the thyroid gland may be mediated through other endocrine systems, notably the pituitary and adrenal. According to Marotta et al. (15), altitude exposure may be accompanied by increased adrenocortical activity. Administration of cortisone to man in doses of 100 mg. or more has been shown to produce a mild to moderate depression in PBI values (19). Hypophysectomy reduces thyroidal I^{131} uptake in rats by as much as 88%, with the maximal effect occurring 5 or 6 days after the operation (18).

The effects of stress on the function of the thyroid gland appear to vary widely with the types of stress applied. Williams and associates (26) reported lowered PBI and I^{131} uptake in rats in response to trauma (application of a tourniquet to the leg), cold ($5^{\circ}\text{C}.$), heat

(38° C.), and Adrenalin injection. In contrast, Falconer and Hetzel (6) reported increased PBI levels in sheep exposed to barking dogs and exploding fireworks. Clinical studies in humans suggest that response of the thyroid gland to stress may not be as great in man as it is in animals. Several investigators have found no change in the PBI of patients undergoing major surgery, medical students preparing for examinations, athletes during football games, and patients with myocardial infarcts (5, 25, 26). They did report, however, that serious chronic illness and malnutrition lowered PBI levels.

Attempts to measure thyroid function usually include one or more of the following parameters: basal metabolic rate (BMR), serum cholesterol level, thyroid avidity for radiiodine, plasma PBI, and measurements of available thyroid hormone-binding sites in the plasma.

From the literature, it appears that the function of the thyroid gland is probably modified by hypoxia, although information on the effects of exposure for periods of longer than one week is almost entirely lacking. In the dog, the thyroid uptake of I^{131} seems to be an acceptable indication of thyroid function, particularly when the dietary intake of iodine is controlled. Other common tests are less reliable in dogs, but the PBI and the resin T3 uptake tests, when used in combination, may give a satisfactory estimate of the status of the thyroid. The exposure of conscious dogs to a pressure of one-half atmosphere induces an adrenocortical response. The duration of this response and the degree to which it influences thyroid function remain to be determined. These findings emphasize the need for more study of the long-term effects of continuous altitude exposure on the thyroid gland.

Since extended manned space flights may require continuous exposure of the crew to less than normal atmospheric pressures, it would be of considerable medical importance to know what changes in thyroid function could be directly attributable to the influence of altitude. The objectives of the present study were:

1. To determine if extended exposure to ambient air at a pressure of one-half atmosphere is

accompanied by significant changes in some commonly used parameters of thyroid function.

2. To compare gross and microscopic anatomy of the thyroid, adrenal, and pituitary glands of altitude-exposed animals with that of control animals maintained at ground level.

3. To attempt to correlate adrenocortical activity with the results of the thyroid function tests.

II. SUMMARY

Iodine-131 uptake and resin T3 uptake tests in dogs continuously exposed to a simulated altitude of 18,000 feet indicated that measurable changes in these parameters may exist after the animals have become acclimatized to low pressure environments. Altitude-exposed animals had higher thyroid uptake of I^{131} and lower resin T3 uptake than the values for ground level controls. An explanation of these results on the basis of the role of oxygen in thyroid hormone synthesis is offered. No significant difference in peripheral blood hydrocortisone levels was noted, thus suggesting that the observed thyroid function changes were unrelated to an adrenocortical response to stress.

The changes observed in the results from the thyroid function tests were not accompanied by any alterations in gross, microscopic, or ultrastructural anatomy of any of the tissues studied at necropsy. The results of this study indicate that some long-term alterations in thyroid function might be expected in extended space flights under hypobaric conditions and that controlled observations in humans under similar conditions might be useful.

III. MATERIALS AND METHODS

Six littermate pairs of 7-month-old, male beagles, procured from commercial sources, were used in this study. All dogs were catheterized and de-barked as described below. They were then placed in cages in the altitude chamber at ground level for one week to allow them to recover from surgery and to become accustomed to the environment of the chamber.

The diet from the time of their arrival at the facility until the conclusion of the experiment consisted of i/d Prescription Diet. The average daily intake of iodide was estimated to be approximately 80 μ g. per dog.

To facilitate the collection of blood samples, a 15-gage polyvinyl catheter was permanently implanted for a distance of 5 inches into the right jugular vein of each dog. The free end of the catheter was passed subcutaneously to the dorsal aspect of the neck where it was brought out through the skin. The catheter was filled with heparinized saline solution, capped, and taped to the skin. All surgery was performed aseptically under pentobarbital sodium anesthesia. While the animals were under anesthesia, a bilateral ventriculocordectomy was also performed.

Identical altitude chambers were used for experimental and control groups. Each chamber was a rectangular steel structure containing two compartments. The interior of each was 7 feet long, 6 feet wide, and 7 feet 3 inches high. The chamber had a single outside entry and a single door which connected the two compartments internally. The floors of the compartments were stainless steel, which extended 4 inches up the side walls. One 18- by 18-inch window was provided on each door, and an 18- by 48-inch window was provided in each side wall. Both compartments were equipped with outlets for oxygen. The compartments could be operated either jointly or independently, and were capable of evacuation to simulate any altitude between ground level and 100,000 feet.

Continuous-flow ventilation of the compartments was provided, as well as a cooling system capable of maintaining any preset temperature from 60° F. to ambient temperature. Each compartment was illuminated by four 60-watt fluorescent bulbs. Gages were provided for monitoring temperature, humidity, barometric pressure, and partial pressures of oxygen and carbon dioxide in each compartment.

All dogs were kept in two-compartmented, fiber glass cages with internal dimensions of

33 by 28 by 28 inches. The temperature was maintained at a constant 75° F. in both compartments. Air flow and illumination were the same in each compartment.

Each dog was offered 1 lb. of the diet daily. If any dog failed to consume the entire amount in 1 day, the remaining portion of the diet was weighed and that amount of food was deducted from the next day's ration of his littermate. Thus, a 24-hour delayed, paired feeding schedule was in effect. Fresh water was provided daily. Daily body weights were recorded.

Personnel entering the chamber wore oxygen masks and protective clothing consisting of surgical gowns, rubber gloves, and plastic shoe covers. Radiation levels in the chamber were monitored by a radiation safety technician. The floors and side walls of the chamber were covered with heavy-duty plastic sheeting, which was replaced if it became contaminated.

The chamber compartment containing the 6 experimental animals was evacuated to 12,000 feet, while the adjoining compartment housing the paired littermates of the experimental animals was maintained at ground level. The simulated altitude in the experimental compartment was increased 2,000 feet per day until 18,000 feet was reached, then held at that altitude for 33 days.

The iodine uptake tracer was carrier-free NaI^{131} given orally in gelatin capsules at a dose of approximately 25 μ c. per dog. The activity of each capsule was measured immediately preceding administration. One capsule was retained as a counting standard, and the amount given to each dog was calculated as a proportion of this standard.

The percent thyroid uptake of I^{131} (corrected for physical decay) was computed according to the formula:

$$U = \frac{(\text{Net thyroid counts})}{(\text{Net standard counts})} \times \frac{(\text{Neck correction factor} \times 100)}{(\text{Proportion of standard administered})}$$

A portable detector probe consisting of a 2-inch-thick thallium-activated sodium iodide crystal and a photomultiplier tube was used. The crystal was shielded by a 1/2-inch-thick lead sleeve, and collimated by a 2 1/4-inch lead cone with an opening 2 inches in diameter. A rigid wire extension from the probe served as a positioning device to maintain a constant crystal-to-skin distance of 8 inches. The amplifier-scaler was a Baird-Atomic, model 138, equipped with a Baird-Atomic power supply, model 312A.

In vivo monitoring was accomplished with the dog in dorsal recumbency on a V-shaped dog board. The animals were trained to accept the counting procedure as a matter of routine before the start of the experiment. The probe was positioned vertically over the larynx 8 inches from the skin, and a 1-minute count was taken. A 1-minute count over the rump of the animal was made to determine the body background radiation. The rump count was subtracted from the neck count to give the net thyroid count.

To establish a correction factor for radiation absorption and scatter by the tissues of the neck, a beagle-size mongrel was killed 4 days after the administration of 25 μ c. I^{131} ; the thyroid glands were removed, and their radioactivity measured in air at a distance of 8 inches from the crystal.

$$\text{Correction factor} = \frac{\text{In vitro counts—Air background}}{\text{Net in vivo counts}}$$

Iodine-131 is a beta-gamma emitter with beta energies of 0.26 to 0.81 Mev and a principal gamma energy of 0.36 Mev. It decays with a half-life of 8.06 days to the stable Xe^{131} .

Single-dose uptake determinations for I^{131} were made on each dog at the following times:

1. Twenty-one days before entering the altitude chamber.
2. Immediately after the experimental animals reached 18,000 feet simulated altitude.
3. Twenty-one days after exposure to the simulated altitude of 18,000 feet.

After administration of the isotope, external monitoring was performed at 4, 8, 12, and 25 hours, respectively, and every 24 hours thereafter until radioactivity counts from the thyroid were less than twice background counts. Seventy-two hours before the end of the experiment, all animals were given a single dose of approximately 25 μ c. I^{131} .

Blood samples were withdrawn by removal of the catheter cap and insertion of a blunted 18-gage needle into the catheter. The heparinized saline solution in the catheter, along with 2 or 3 ml. of blood, was aspirated and discarded. A clean 10-ml. syringe was attached, the sample withdrawn, and the catheter refilled with heparinized saline solution and recapped. A 20-ml. blood sample was drawn from each dog 1 day before decompression and immediately after 18,000 feet simulated altitude was reached. Thereafter, samples were taken approximately every 6 days until the conclusion of the experiment. Packed cell volume (PCV) was determined by the microhematocrit method. All blood samples were allowed to clot at room temperature and centrifuged, and the serum removed and placed in a freezer at -18° C.

The ability of the plasma protein to bind thyroid hormones was estimated by measuring the transfer of I^{131} -labeled T3 to an anionic resin-impregnated sponge exposed to the test sample. A commercially available kit (Trio-sorb T3 Diagnostic Kit) was used, following the procedure described by McAdams and Reinfrank (14).

Serum PBI content was determined by a fully automated (Technicon AutoAnalyzer) modification of the ceric ion reduction method (1). This procedure required a 2-ml. sample. The inorganic iodide was first removed by an anionic exchange resin, and the bound iodide released by digestion with sulfuric, nitric, and perchloric acids. The digested material was diluted with water and a sample was taken. Arsenous acid and ceric ammonium sulfate were added to this sample, and the mixture was heated to 55° C. The transmittance at 410 m μ was measured in a colorimeter. The iodide in

the digested serum catalyzed the reduction of the yellow ceric ammonium sulfate by the arsenous acid. The color change in the solution was directly related to the amount of protein-bound iodide in the serum sample. Standard samples with known iodide concentration were tested to establish calibration curves. The variability of replicate samples of standard serum was no greater than 5%.

The method used for analysis of serum 17-OHCS was Peterson's modification of the Porter-Silber technic (17), which is based on the fact that hydrocortisone reacts with phenylhydrazine to yield a yellow-colored product. The maximum error in replicate samples containing 5 μ g. of hydrocortisone per 100 ml. of serum is 5%. With higher concentrations, the error is somewhat smaller.

At the termination of exposure, all dogs were given a lethal dose of pentobarbital sodium, and a thorough necropsy was performed. The thyroid, adrenal, and pituitary glands were removed and weighed. Iodine-131 activity in the thyroid glands was counted in vitro at a distance of 8 inches from the crystal. In vitro counts were compared with in vivo counts to determine correction factors for neck absorption and scatter. Sections of all three glandular tissues were fixed in natural buffered formalin for histopathologic processing and in 4% glutaraldehyde for electron micrography. The ratio of colloid, follicle cells, and stroma in the thyroid glands was noted, as well as any other significant microscopic features.

The activity of the follicle cells at the ultrastructural level was determined by a system of

random sectioning and blind grading. Three 1-mm. blocks of tissue were cut from different areas of the gland, and three rectangular sections were cut from each block. Electron micrographs were taken of the center and each corner of every section, giving a total of 45 micrographs per gland. Each micrograph was graded either high, medium, or low in each of the five categories listed in table I. Although the relationship of ultrastructure to the endocrine function of the thyroid gland has not been determined, these criteria represent a sampling of most current opinion (9, 16, 20, 27). The identity of the sections was unknown to the grader, and the results were tabulated by a disinterested person.

IV. RESULTS

At the start of the altitude exposure, all dogs had normal appetites and activity. Dog 1B removed its jugular catheter before the altitude exposure began, and dog 5A lost the catheter after 15 days' exposure. The catheters were not replaced, and all blood samples from these animals were drawn by puncture of the left jugular vein. Catheters in the other animals functioned well throughout the experiment.

A slight decrease in the mean body weight of the experimental dogs was observed in the time between their introduction into the chamber and the actual altitude exposure (fig. 1). No decrease occurred in the control animals. During the experiment, however, the mean body weight of the experimental animals remained fairly stable in the first half of the exposure period, then gradually increased until

TABLE I
Grading criteria for thyroid secretory activity

	High activity	Low activity
Nucleus	Large, oval, low electron density, finely granular	Irregular size and shape, high electron density, coarsely granular
Cellular inclusions	Many secretory granules	Few secretory granules
Golgi apparatus	Large, extensively developed	Small, unapparent
Cell shape	High cuboidal epithelium	Low, flattened epithelium
Endoplasmic reticulum	Ribosomes distinct, cisternae large	Ribosomes less distinct, small cisternae

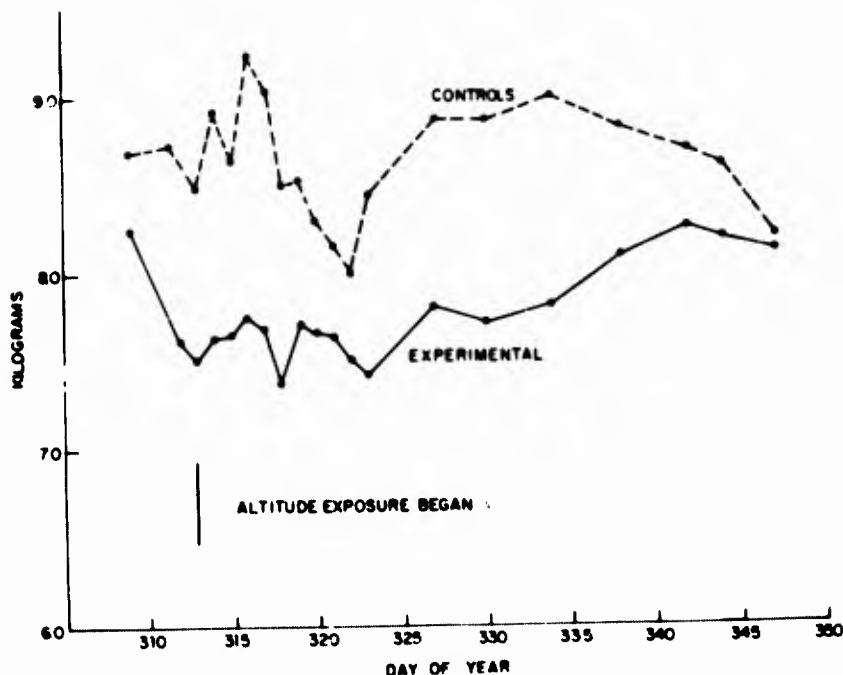


FIGURE 1
Mean body weight.

it was not significantly different from that of the controls.

Serum 17-OHCS levels of both groups during the experiment are shown in figure 2. The data were examined in a three-way analysis of variance program. Differences between experimental groups, between pairs of animals, and in individual animals with respect to time were found to be not significant. The range of values was from less than 1.0 $\mu\text{g.}/100\text{ ml.}$ serum to over 12 $\mu\text{g.}/100\text{ ml.}$ There was considerable fluctuation in successive observations on each animal.

Packed cell volumes are shown in figure 3. Before the altitude exposure, no difference was seen between groups. On the third day of exposure, the PCV of the experimental group was significantly greater than that of the controls and remained so for the duration of the experiment with no further significant increase. Dogs in both groups had considerable daily fluctuation in PCV values.

PBI values obtained from both groups early in the experiment were extremely high with many above 20 $\mu\text{g.}/100\text{ ml.}$ The possible effect of handling and storage on the serum samples was considered, and standard serums were handled, frozen, and stored in the same manner as the experimental samples. No appreciable change was noted in the standard serums.

No apparent difference was noted between the two groups, but the data were not subjected to statistical analysis nor used to calculate the "free thyroxine index" owing to the extremely dubious results.

The mean daily thyroidal I^{131} uptakes in both groups 21 days prior to the altitude exposure were almost identical, with peak uptakes of approximately 7% occurring 96 hours after administration. A three-way repeated measurements analysis of variance was run to test all I^{131} uptake results. In the pre-experimental uptake studies, no significant difference was noted either between experimental conditions

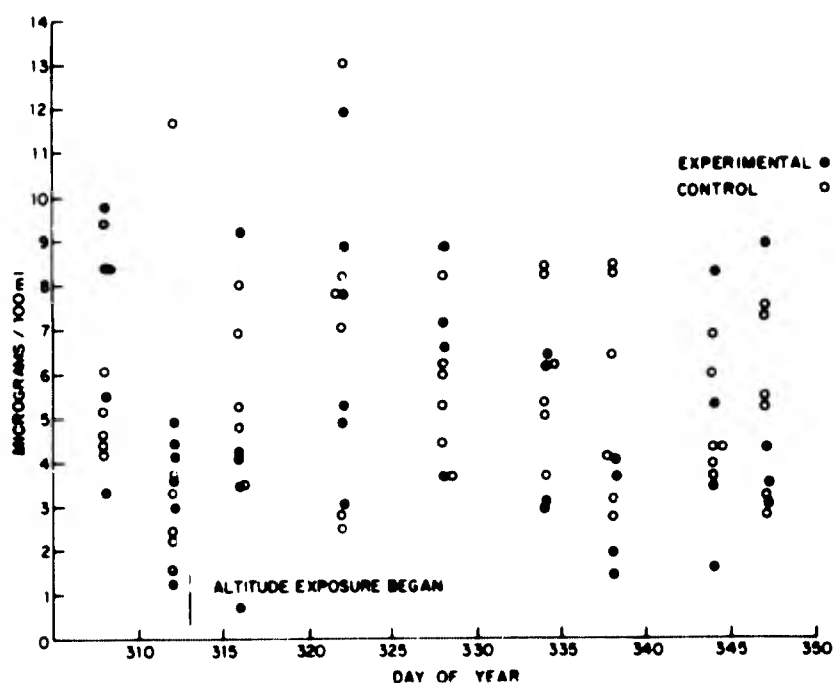
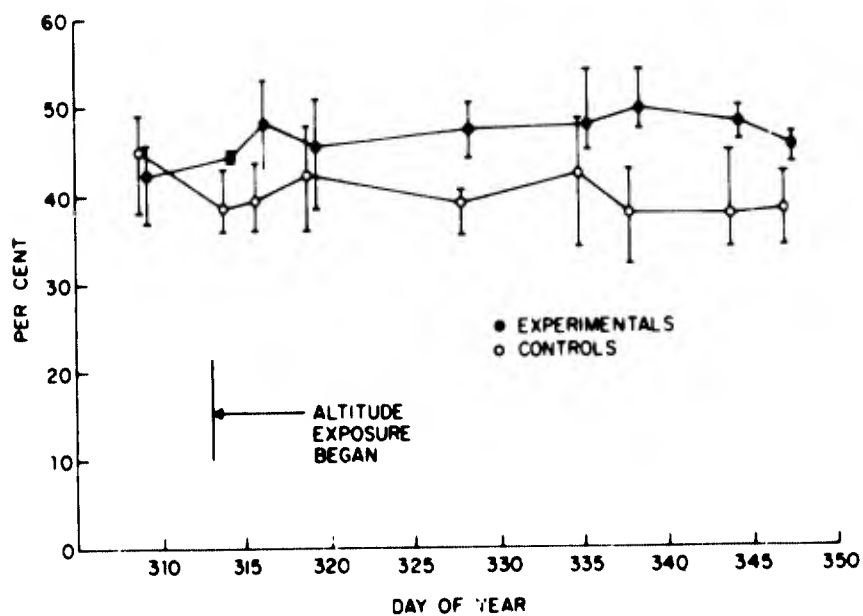


FIGURE 2
Serum 17-hydroxycorticosteroids.



or between littermate pairs. In the I^{131} uptake test run immediately after exposure of the experimental animals to 18,000 feet simulated altitude, these dogs showed higher mean daily uptake values than those of the controls (fig. 4). The difference between the two groups was significant at the 10% level in the analysis of variance. Data from the pairs in which the experimental animals died were not used in the analysis.

Mean values of the experimental dogs after 21 days' exposure were still lower than those of the controls. Variability, however, was considerable, and the difference between groups was not significant in the analysis of variance.

At the start of the altitude exposure, both groups had mean resin T3 uptakes of approximately 50%. As the experiment progressed, values for the experimental dogs remained fairly constant, whereas a gradual increase occurred

in the values for control dogs. A difference between the two groups was apparent on the fifteenth day of exposure (fig. 5). The increase in values with time for control animals was significant at the 5% level, while the difference in values between experimentals and controls was significant at the 1% level.

On gross postmortem examination, all animals with implanted catheters showed some degree of subacute metastatic pneumonia and thrombosis of the anterior vena cava and right atrium. The single control animal which removed its catheter at the start of the experiment had no such changes. Lesions ranged from mild to moderate with no significance in the distribution between experimental and control animals. All other organs were grossly normal in both groups. Organ weights are given in table II. There was no difference in mean values as shown by the Student's t-test.

On microscopic examination, there was a fibrinous exudate in the pulmonary alveoli, mixed inflammatory cell infiltration of perivascular spaces, and occasional septic thrombosis of pulmonary vessels. Both groups had occasional foci of inflammatory cells in the liver, and slight to mild hyperplasia of splenic

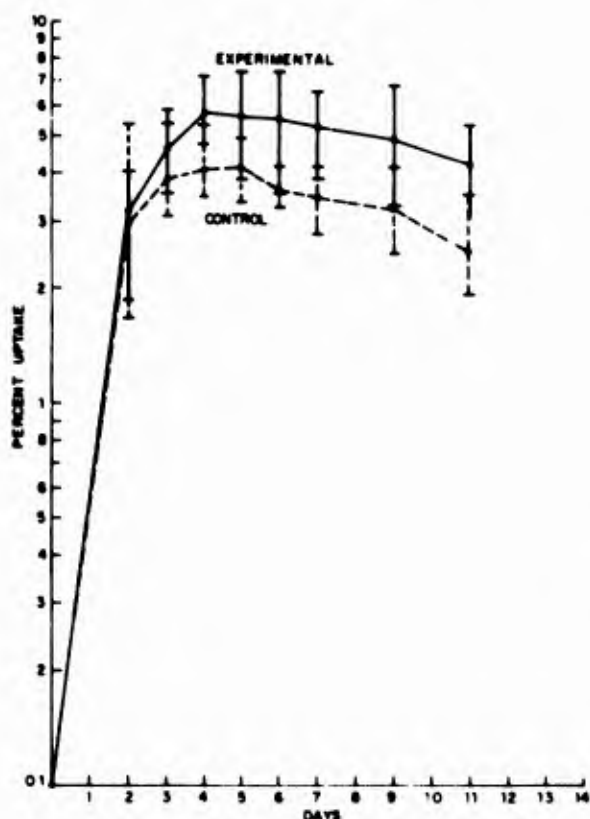


FIGURE 4

Iodine-131 uptake first week of altitude exposure.

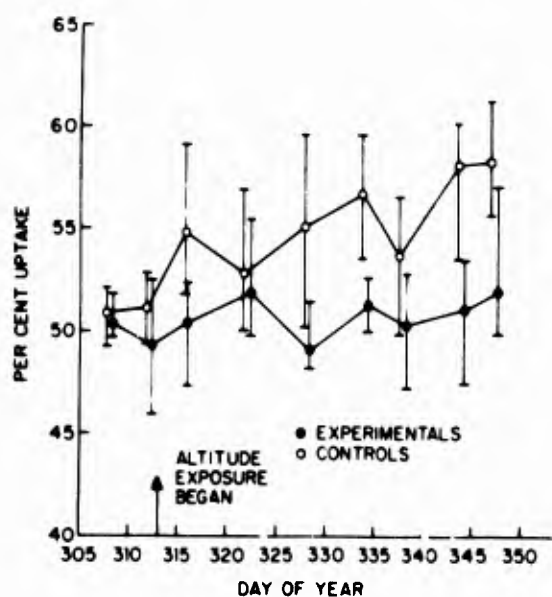


FIGURE 5

Resin sponge T3 uptake.

follicles. All thyroid glands had a normal histologic appearance with a wide range of follicle sizes and cell shapes noted in each gland (fig. 6). Thyroid glands from the two groups were compared on the basis of colloid/follicle cell ratio, and no difference between groups could be identified. Adrenal and pituitary glands of the experimental animals were histologically indistinguishable from those of the controls.

Figure 7 is an electron micrograph of a thyroid section illustrating the structures used for grading secretory activity. Results of the grading are given in table III. For all five cell characteristics, no difference between groups was apparent.

V. DISCUSSION

During the course of the experiment, it became apparent that the use of permanent, indwelling, jugular catheters to draw samples of venous blood was not the most desirable technic under the given experimental conditions. The ease with which a jugular venipuncture could

be accomplished on animals trained to lie motionless on a dog board demonstrated that no noticeable decrease in amount of handling or agitation of the animals was obtained by the use of the catheters.

The fluctuations in packed cell volumes may be explained by the fact that the animals were not splenectomized. The early increase in the PCV of the altitude-exposed animals may indicate either an immediate release of erythrocytes into the circulating blood or a water shift due to hyperventilation. Since no further significant increase in PCV occurred after the third day of exposure, it is apparent that the hematopoietic system was able to adjust rapidly to a one-half atmosphere environment. Reticulocyte counts during this period might have been helpful.

Serum concentrations of 17-OHCS were generally lower than those observed in humans (17). Since no difference in circulating 17-OHCS levels was seen between groups at any time during the experiment and no gross or histologic differences in the adrenal glands

TABLE II
Organ and body weights (in grams)

Group	Pair						Mean	S.D.	Significance
	1	2	3	4	5	6			
Thyroid	A	0.6518	0.6847	—	—	0.4323	0.6418	0.6026	NS
	B	0.7063	0.5527	0.7467	0.6382	0.6828	0.5903	0.6528	
Adrenal	A	1.1430	0.7529	—	—	0.6669	0.7237	0.8217	NS
	B	1.1540	0.7780	1.0620	0.7097	0.8810	0.7394	0.8814	
Pituitary	A	0.0778	0.0530	—	—	0.0521	0.0420	0.0562	NS
	B	0.0605	0.0558	0.0548	0.0470	0.0551	0.0368	0.0516	
Total body	A	9,030.0	7,670.0	—	—	7,670.0	7,900.0	8,120.0	NS
	B	9,030.0	7,450.0	7,450.0	8,350.0	8,570.0	7,900.0	8,180.0	

A — Experimental.

B — Control.

NS = Not significant at the 10% level

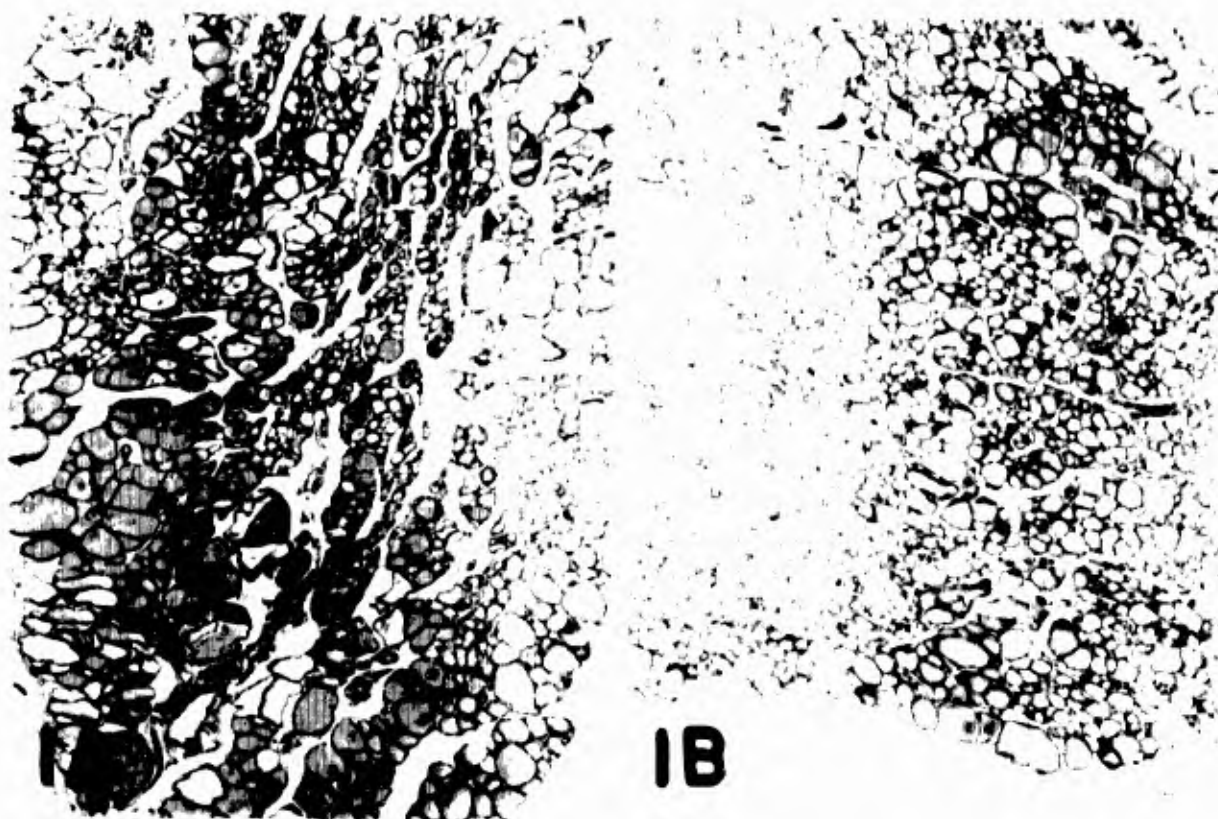


FIGURE 6

Thyroid glands from pair 1. A—Experimental; B—Control.

were observed at necropsy, it may be concluded that adrenal function was not affected by the experimental conditions unless an extremely transitory response occurred within the first 24 hours of altitude exposure.

Erroneously high PBI values may be caused by exposure of the animal to any of a number of iodinated compounds or by contamination of the test sample. In the present study, the correct values obtained in standard samples handled identically with test samples tended to rule out the latter possibility. The elevated results early in the experiment, followed by a steady decrease in most animals, suggested a single exposure of the test animals to some PBI-elevating factor. Contact with such compounds was specifically avoided, but the possibility of an inadvertent exposure during the 5 months the animals were observed could not be definitely ruled out.

The observed percentages of thyroidal I^{131} uptake were lower than the 10% to 40% reported by other investigators (11, 13). This may have been a result of the continuous intake of more than adequate amounts of stable iodine in the diet which competed with the tracer for uptake by the thyroid. The combination of higher I^{131} uptake and lower resin T3 uptake in the altitude-exposed dogs is somewhat confusing, but might be explained on the basis of some evidence of the role of oxygen in thyroid synthesis. It is generally accepted that iodine trapped by the thyroid gland must be oxidized before combination with the tyrosine moieties in thyroglobulin can occur. The lack of oxygen inhibits this reaction in vitro. Oxygen may also be important in the coupling of two molecules of diiodotyrosine (DIT) to form thyroxine. It has been proposed that the mechanism of the coupling reaction is the combination of DIT with 4-hydroxy,3,5-diiodophenylpyruvic acid

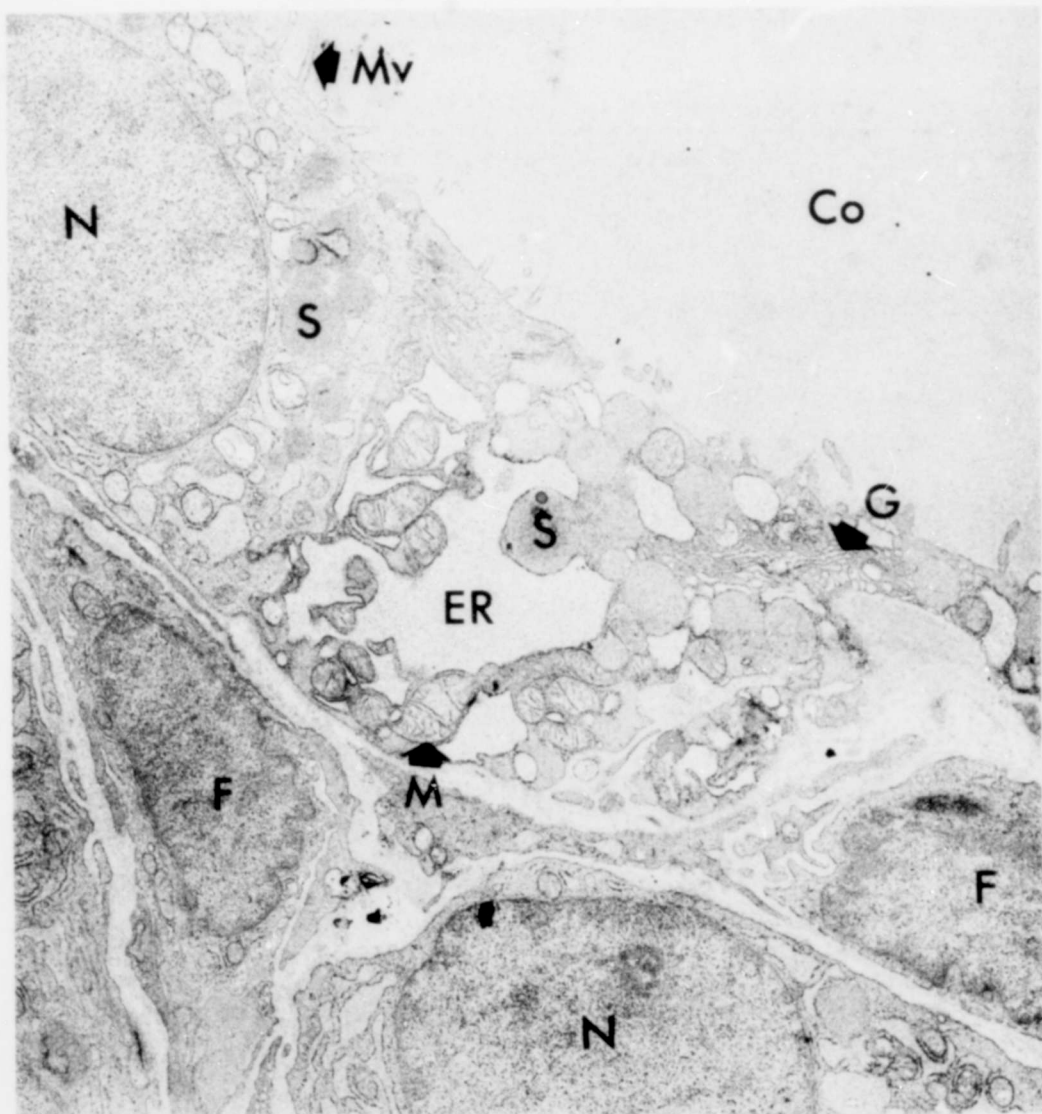


FIGURE 7

Electron micrograph of canine thyroid gland (3100 $\times$). Co—colloid; N—Follicle cell nucleus; S—Secretory granules; G—Golgi apparatus; F—Fibroblast nuclei; M—Mitochondria; Mv—Microvilli; and ER—Endoplasmic reticulum cisterna.

TABLE III

Grading results for thyroid secretory activity

	High	Medium	Low	Ungraded
Nucleus	Percent			
A (174)*	15.5	47.2	24.1	12.1
B (262)	20.6	60.7	14.5	4.2
Golgi				
A (175)	12.6	45.2	37.2	5.0
B (261)	21.1	44.4	31.8	2.7
Inclusions				
A (174)	13.8	47.1	36.2	2.9
B (264)	13.6	49.2	35.2	2.0
Cell shape				
A (172)	14.5	48.2	31.4	5.9
B (266)	15.0	55.0	27.4	2.6
Endoplasmic reticulum				
A (172)	8.7	37.2	46.5	7.6
B (260)	7.7	45.4	42.0	4.9

A = Experimental.

B = Control.

*Number of sections.

(DIHPPA) (21). This reaction also proceeds only under aerobic conditions in vitro. Another important reaction in thyroid metabolism is the deiodination of the nonhormonal iodinated proteins remaining after the degradation of thyroglobulin to thyroxine. This reaction provides free iodide which may be incorporated again into a tyrosine radical. The role of oxygen in this reaction has not been proved, but it is possible that the reaction does proceed best under aerobic conditions.

If the hypoxia induced by exposure to altitude did cause an initial reduction in hormone synthesis by inhibiting tyrosine iodination and DIT coupling, the lower level of circulating hormone as measured by the resin T3 uptake

could be explained. This lower level could stimulate iodide trapping in the thyroid gland via the thyroxine-TSH negative feedback system, resulting in increased I^{131} uptake. Decreased deiodination of thyroglobulin fractions would also enhance I^{131} uptake by reducing the amount of endogenous iodide competing with the administered tracer. The results do not rule out the possibility of change in the peripheral utilization rate of thyroxine.

The resin T3 uptakes seen in the dogs were approximately 67% higher than normal values for humans (14). This elevation might be an indication of the presence of nonhormonal PBI as suggested by Kaneko (10). The resin T3 uptake of the control animals gradually increased during the experiment, while that of the experimentals remained the same. This increase in the controls could reflect a gradual thyroidal adjustment from an outdoor to an indoor environment which was inhibited by the hypoxia in the altitude-exposed animals.

The lack of such a change in the altitude-exposed animals reflected persistence of a relative increase in available T3 binding sites in the serum of these animals. Such an increase would be consistent with the hypothesis that exposure to altitude caused a reduced hormone synthesis with resulting decrease in serum hormone levels.

The similarity in organ weights and histologic appearance of the two groups suggested that functional changes can occur in the thyroid gland without any gross or microscopic manifestations. Since thyroid follicles in almost all stages of activity could be demonstrated in every gland observed, the difficulty in characterizing the activity of an entire gland by electron microscopy became readily apparent. Differences in thyroidal ultrastructure between the two groups, if present, were too small to verify statistically with a sample size of 45 sections per gland.

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13. ABSTRACT

Six male beagle dogs were maintained on ambient air at one-half atmosphere for 33 days and were monitored for protein-bound iodine (PBI), thyroid I¹³¹ avidity, plasma triiodothyronine uptake, and plasma 17-hydroxycorticosteroids. Data were compared with those from littermate controls held at ground level.

Increased I¹³¹ uptake and reduced triiodothyronine uptake were observed in the altitude-exposed dogs, while no change in the peripheral blood hydrocortisone level was seen. No difference in the gross, microscopic, or ultrastructural anatomy of the thyroid glands of groups was noted.

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