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Effects of Methylthiouracil on Basal Metabolism Rate and Cholesterol Level in Dog.

By

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INTRODUCTION

Since the clinical introduction of the synthetic antithyroid drugs in the pharmacotherapy of thyrotoxicosis there have been published several clinical and experimental reports concerning the toxic effects of these drugs (3,8,9,10).

The purpose of this experimental investigation was to study the nature and mechanism of the effects of prolonged oral administration of methylthiouracil on basal metabolism rate and cholesterol level in dog.

METHODS

Our experiments were performed on 24 puppies of both sexes, weighing 3-6 Kg kept in metal cage and fed with ground meat, wheat bread and tap water ad libitum.

The physiological parameters: body weight, heart rate, respiration rate, rectal temperature, blood cholesterol, basal metabolism rate and blood cell count were determined beforsm and periodically during prolonged administration of methylthiouracil until the spontaneous death of the animals.

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The body weight, heart rate, respiration rate and rectal temperature were measured daily, whereas cholesterol, BMR and blood cells were determined once a week. The blood sample, for all measurments, was taken in a fasting state from the peripheral veins (basilic or external saphena).

The blood cholesterol was measured by the Bloor-Sackett method (reaction of Liebermann-Burchard).

The basal metabolic rate was determined by the Sanborn closed-circuit Metabograph under a light anethesia induced by I.V. injection of 20-30 mg/Kg pentobarbital (Nembutal) and using a cuffed-endotracheal tube.

The solution of MTU (methylthiouracil) was administered orally by gastric tube, at the dose of 50 mg/Kg daily at 4:00 P.M. 6 days a week until the occurrence of death. Only in the first experiment a dose of 20 mg/Kg and in the three succeeding cases a dose of 100 mg/Kg was used. The autopsy was performed in several instances and the thyroid gland was excised for the histological study.

RESULTS

The survival time of 24 dogs under experiment ranged from 10 to 73 days but only 11 (less than 50%) survived until the third week.

A- Physiological and biochemical disturbances: The results of our measurments as summarized in the Table I demonstrate inconsistent changes of all parameters in a varying incidence and with wide variance. However the decrease of body weight, basal metabolism rate, respiration rate and erythrocyte count showed a statistically significant difference ($P<0.05$) respectively from the first, second and third week (Table I, Fig I), while the changes of blood cholesterol was not statistically significant.

B- Physical manifestations: The loss of body weight as low as 30% accompanied by anorexia and general asthenia were manifested in 16 cases from the second week, but in 6 cases an initial gain of weight ranging from 5 to 18% was developed in the first week and in 2 cases this obesity lasted until the occurrence of death.

A bilateral exophthalmos was developed in 2 cases: the first case after 11 days and total administration of 5.185 g MTU and the second one after 56 days administration of 12.46g MTU (Fig II). A bilaterai corneal opacity was developed in one case at the 12th day after administration of 1.5 g MTU.

The hair loss was manifested in 10 cases from the second week. A cutaneous desquamation was appeared in one case after 34 days and total administration of 6.4g MTU (Fig III).

C- Histological alterations: The circulating erythrocytes showed a low count accompanied by anisocytic and poikilocytic alterations from the first week.

The histological studies of the thyroid gland revealed a diffuse hyperplasia in 11 cases (out of 12 cases examined) in which the death occurred within 10-73 days after administration of 1.9 - 17.35 g MTU (Fig IV,V).

DISCUSSION

The physiological and histological alterations observed under the influence of prolonged administration of MTU can be explained mainly on the basis of the two following mechanisms.

1- Hypothyroidism produced by the inhibitory action of MTU on the biosynthesis of the thyroid hormones.

The bradypnea, low BMR, bradycardia, weight gain, cutaneous manifestations, thyroid hyperplasia and exophthalmos altogether are good indications of the drug - produced hypothyroidism.

The decrease of BMR produced by administration of the thiouracil derivatives has been reported by numerous investigators in hyperthyroidic patients (4) as well as in experimental animals such as rat (1,7).

The cutaneous manifestations have also been reported as one of the side-effects of the thiouracil derivatives (3,9,10).

Table I - The variations of the physiological parameters.

	before	First week		Second week		Third week		% of maximal change
Number of dogs	24	24		24		11		
Parameters	mean±S. D.	mean±S.D.	p	mean±S.D.	p	mean±S.D.	p	
Body weight (Kg)	4.5±0.79	4.3±0.82	>0.40	4±0.79	<0.025*	4.1±0.83	>0.20	-12
Rectal temp. (C)	37.5±0.68	37.7±0.57	>0.30	37.8±0.73	>0.20	38.1±0.76	<0.025*	+1.6
Heart rate	130±14.59	126±9	>0.20	127±13.37	>0.40	123±10.29	>0.50	+3.1
Respiration rate	49±23.36	42±9.39	>0.20	35±9.69	<0.005*	29±6.55	<0.01*	-40.9
BMR(O^2CC/min/Kg)	11±1.89	9.9±2.28	<0.05*	9.8±1.45	<0.05*	10.6±1.87	>0.70	-11
Blood chol. (g%)	0.210±0.03	0.192±0.03	>0.20	0.218±0.03	>0.60	0.213±0.003	>0.90	-8.6 +3.8
Erythrocytes	4,323,000	4,115,000	>0.80	4,081,000	>0.50	3,516,000	<0.005*	18.7

* denotes statistical significance.

The thyroid hypeyrplasia, as it is a common and well-known reaction of the antithyroid drugs particularly of the thiouracil derivatives in thyrotoxicosis (4,5,8) has been produced experimentally in rat by administration of allyl thiourea (1). The development of thyroid hyperplasia associated with signs of hypothyroidism is explaind on the basis of a glandular compensatory mechanism induced by hypersecretion of pituitary TSH and feed-back mechanism caused by inhibitory action of the antithyroid drugs on the iodothyronil biosynthesis in the thyroid glands.

The development of exophthalmos was very likely due the thyroid feed-back mechanism and consequent hypersecretion of TSH reported by other investigators in rat, (7) guinea-pigs (2) and man (6).

2- Toxic effects of MTU - The general asthenia and emaciation can be attributed to hypothyroidic anorexia and toxic effects of the drug.

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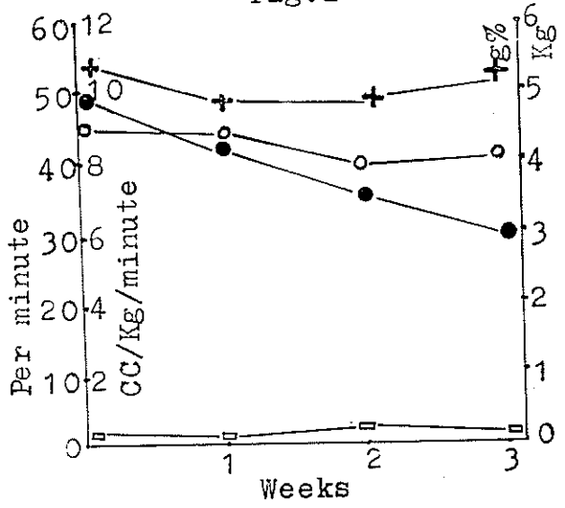
Fig. I



+ O_2 (BMR)
● Respiration Rate
○ Weight
– Cholesterol

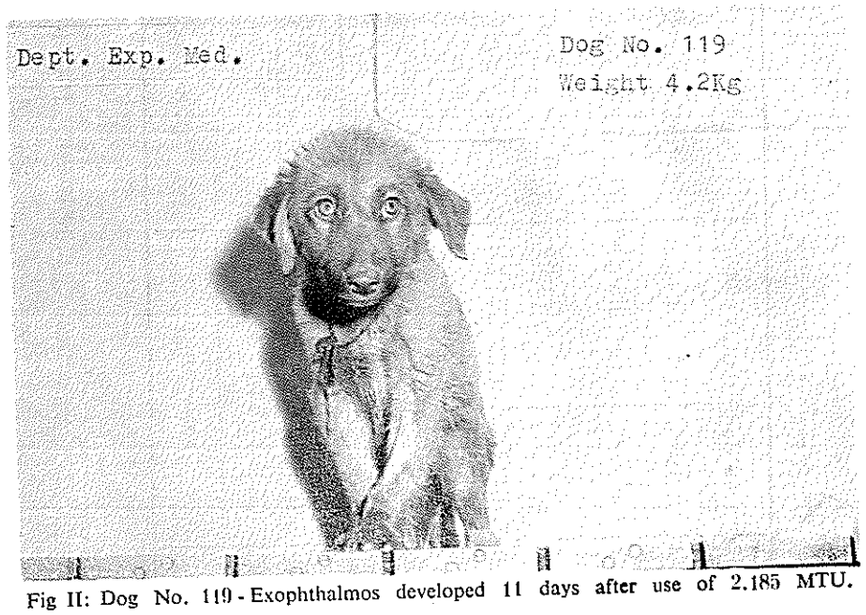


Fig II: Dog No. 119 - Exophthalmos developed 11 days after use of 2.185 MTU.

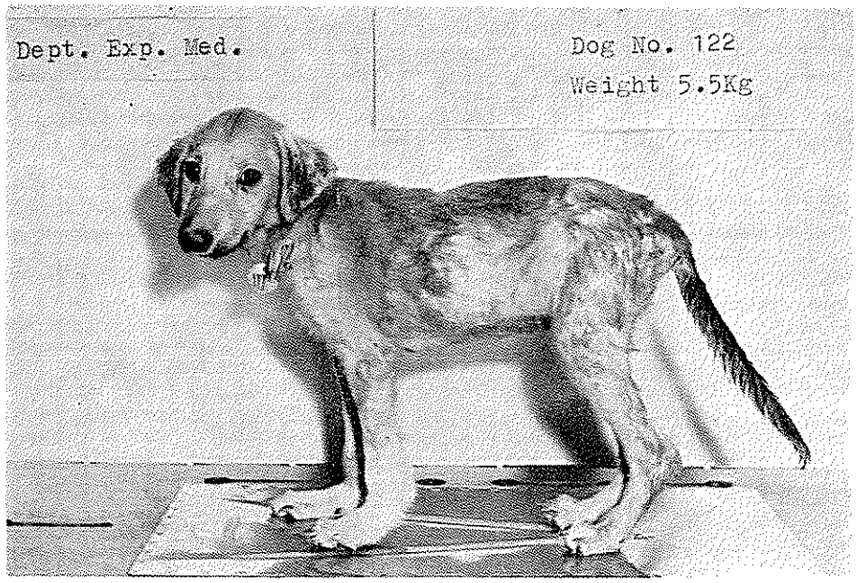


Fig III: Dog No. 122 - Emaciation and hair loss particularly noticed at the flanks, 34 days after use of 6.4 g MTU.

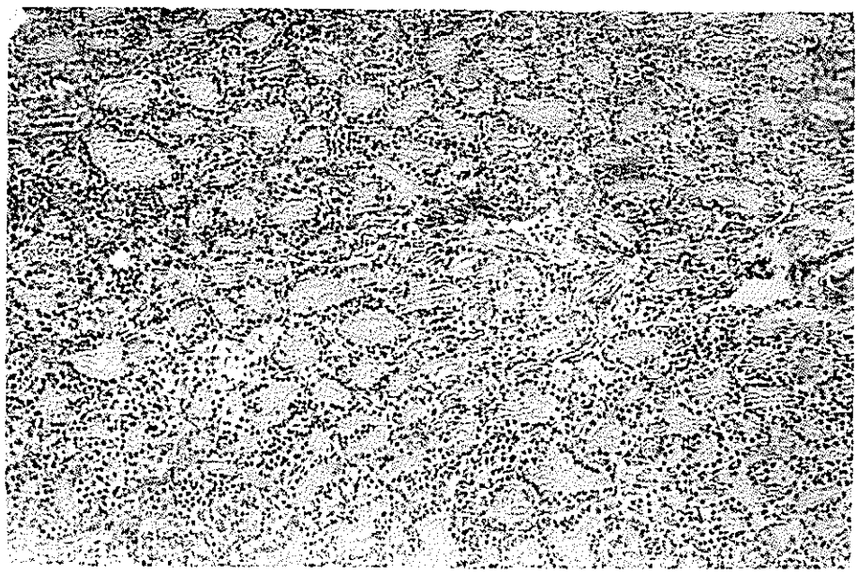


Fig IV: Dog No. 119–Hyperplasia of the thyroid gland after use of 8.57 g MTU.

Fig V: Dog No. 101—The thyroid glands excised 21 days after use of 2.683g MTU.

Summary

The effects of prolonged administration of methylthiouracil were studied on several physiological parameters pertinent to the thyroid function in dog.

Though the individual variations of the measured parameters were not consistent but the statistical differences of diminution of basal metabolism rate, respiration rate and erythrocyte count. were significant

Brief explanations for the mechanism of the pathophysiological findings were presented.

Resumé

Nous avous etudié expérimentalment les effets de l'administration orale prolongée de methylthiouracil sur quelques paramèters physiologiqnes relatives aux fonctions de la glande thyroide chez le chien.

Quoique les variations individuelles des paramètres mesurées n'ont pas été constantes, mais la diminution du métabolisme basal, la taux respiratoire et le nombre des erythrocytes e été significative du point de vue statistique.

Le mcanisme pathophysiologique des altérations observées est discuté brièvement.

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Bacteriological Survey of Urinary Tract Infection ✡

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Difficulties in the diagnosis of infections of the urinary tract are common, and it is important that satisfactory criteria be established that may prove helpful to the clinician in making such diagnosis. It is well established that urether harbours some pathogenic organisms in its normal flora and these are grown on culturing urine specimens. Therefore the more presence of any given pathogenic bacteria in urine is not an adequate basis for ruling it in or out as a cause of clinical urologic disease. The bacterial count of urine has offered one means of resolving this problem (2,4). Thus quantitative study of the baccterial flora of freshly obtained urine, as an added tool to separate true bacteriuria from contamination that occurs during the collection process

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