CLXXVI. THE EFFECT OF ADMINISTRATION OF CALCIFEROL ON THE INCREASED CALCIUM EXCRETION INDUCED BY THYROXINE.

BY LEONARD IRVING PUGSLEY AND EVELYN ANDERSON.

From the Department of Biochemistry, McGill University, Montreal.

(Received June 26th, 1934.)

It has been shown by a number of workers who have followed the excretion of calcium by rats during the administration of irradiated ergosterol, that a decrease in the faecal calcium occurs along with an increase in the excretion of calcium in the urine [Watchorn, 1930; Pugsley, 1932; and others]. Taylor and Weld [1932] showed that a decrease in the faecal calcium of dogs which had received desiccated thyroid occurred during ergosterol administration. The efficacy of irradiated ergosterol therapy in correcting the negative calcium balance in cases of clinical hyperthyroidism has not been so conclusive. Tibbets *et al.* [1932] found no effect, while Hansman and Wilson [1934] found an improvement in the calcium balance. Pugsley and Anderson [1934] have shown that a decrease in the faecal calcium can be produced by the administration of irradiated ergosterol to rats which showed a high faecal excretion of calcium as a result of feeding desiccated thyroid. Although the calcium balance of these rats did not become definitely positive as a result of the ergosterol administration owing to the simultaneous increase in the excretion of calcium in the urine, we considered this a matter of dosage. In this communication we are able to show that a definite improvement in the balance can be obtained when the dosage of the two opposing factors is adequately controlled.

Methods.

The diet, feeding of the rats and analytical methods were the same as those previously described [Pugsley and Anderson, 1934]. Schering-Kahlbaum's thyroxine was dissolved in 0.002*N* NaOH and made up so that 1 ml. contained 0.1 mg. of thyroxine. The calciferol was kindly given by Messrs Ayerst, McKenna and Harrison. It was dissolved in corn oil and diluted so that 1 ml. contained 50,000 international units.

Results.

The effect of intraperitoneal injections of 0.2 mg. of thyroxine (1 ml. of the above solution night and morning) per rat per day upon the calcium excretion, calcium balance, metabolic rate and body weight of the rats is shown in Table I. The values represent the average of four rats. The thyroxine injections were begun on the 10th day and continued throughout the experiment. The calciferol was introduced on the 40th day and discontinued on the 60th day. This was administered by allowing 0.1 ml. to drop from a pipette into the rat's mouth (0.1 ml. = 5000 international units per rat daily). It may be noted that, until the administration of the calciferol, a progressive increase in the calcium excre-

Table I. *The effect of administration of calciferol on the increased calcium excretion induced by thyroxine.*

Treatment	Day	Urine-Ca mg./day	Faecal Ca mg./day	Ca balance mg./day	Body wt. g.	% increase in O ₂ consumption
Control period	2	0.01	1.92	+4.32	255	0 (normal)
	4	0.01	1.60	+4.74	257	
	6	0.01	1.52	+5.12	258	
	8	0.01	1.55	+5.24	259	
	10	0.01	1.63	+5.16	259	
0.2 mg. thyroxine daily from the 10th day throughout the ex- periment	12	0.01	1.96	+4.28	254	+31.8
	14	0.03	2.65	+2.94	250	
	16	0.03	3.20	+3.42	246	
	18	0.05	3.72	+3.23	243	
	20	0.08	5.25	+2.47	240	
	22	0.10	4.25	+3.54	240	+48.5
	24	0.13	5.52	+2.18	238	
	26	0.13	4.37	+3.30	234	
	28	0.12	6.44	+1.26	235	
	30	0.12	7.62	+0.06	234	
	32	0.16	6.87	+0.77	232	+46.4
	34	0.16	7.37	-0.25	223	
	36	0.28	7.37	-2.31	221	
	38	0.14	7.50	-2.08	219	
	40	0.17	8.62	-2.39	215	
5000 units calciferol daily	42	0.14	7.37	-0.21	209	+46.4
	44	0.07	5.87	+1.85	206	
	46	0.02	6.87	+0.91	203	
	48	0.10	6.97	+0.73	199	
	50	0.80	4.50	+2.50	197	
	52	1.16	4.25	+2.39	198	+32.6
	54	1.10	3.00	+3.70	196	
	56	1.05	3.15	+3.60	194	
	58	0.94	2.90	+4.00	193	
Calciferol discontinued	60	0.96	3.03	+3.81	193	+26.6
	62	0.52	3.43	+3.85	192	
	64	0.45	6.50	+0.85	191	
	66	0.37	9.25	-1.82	193	
	68	0.35	11.50	-4.05	194	

tion in the faeces occurs, and the calcium balance becomes less positive and finally negative. Upon administration of the calciferol the excretion of calcium in the faeces is definitely decreased within 4 days. It is also noted that the excretion of calcium in the urine does not increase significantly until about the 10th day, and the calcium balance is definitely positive from the 4th day of administration of the calciferol. The rats returned to a negative calcium balance shortly after the calciferol was discontinued.

DISCUSSION.

This work is in agreement with the previous publication of Pugsley and Anderson [1934] in that thyroxine appears to be just as effective as desiccated thyroid in causing an increase in the excretion of calcium in the faeces in rats. It is also a confirmation of the view of Aub *et al.* [1929] that the thyroid hormone has a specific effect upon calcium metabolism. We do not feel, as Hansman and Wilson [1934] have recently suggested, that the effect of hyperthyroidism on calcium metabolism is determined by the degree of hyperparathyroidism, though our experiments do not, of course, disprove the possibility of concomitant hyperparathyroidism in clinical hyperthyroidism.

The effect of calciferol on the increased excretion of calcium in experimental hyperthyroidism points to a specific effect of vitamin D in controlling the retention of calcium. The fact that we were unable to bring the rats into a positive balance in our previous work by the use of irradiated ergosterol we consider to be due to a failure to control the dosage of the two opposing factors.

SUMMARY.

The intraperitoneal injection of 0.2 mg. of thyroxine daily into adult rats leads to a marked increase in the excretion of calcium in the faeces and the establishment of a negative calcium balance. The administration of 5000 international units of calciferol daily by mouth to these rats reduces the faecal excretion of calcium and corrects the negative calcium balance.

Our thanks are due to Prof. J. B. Collip and Dr D. L. Thomson for their assistance and advice.

REFERENCES.

- Aub, Bauer, Heath and Ropes (1929). *J. Clin. Invest.* **7**, 97.
Hansman and Wilson (1934). *Med. J. Australia*, **37**, 81.
Pugsley (1932). *J. Physiol.* **76**, 315.
— and Anderson (1934). *Biochem. J.* **28**, 754.
Taylor and Weld (1932). *Brit. J. Exp. Path.* **12**, 109.
Tibbetts, McLean and Aub (1932). *J. Clin. Invest.* **11**, 1273.
Watchorn (1930). *Biochem. J.* **24**, 631, 1560.