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THE HISTOLOGICAL CHANGES IN THE BONE
RESPONSIBLE FOR THE ACTION OF PARA-
THYROID HORMONE ON THE CALCIUM
METABOLISM OF THE RAT.

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It was reported by Pugsley [1932] that the calcium excretion in rats receiving daily injections of parathyroid hormone¹ was markedly increased during the first 4 days of administration, but returned to a normal or even subnormal level within 8–10 days in spite of continued injections. It was also found by a number of investigators that if parathyroid hormone was given to animals or man over a long period of time it lost its power to mobilize calcium, and in the later stages of the treatment the serum calcium might actually be reduced by the hormone instead of being increased. The explanation of these observations was unknown and it has been assumed that a certain “immunity” is developed against this hormone after a certain period of treatment.

Selye [1932 *a, b*] found that the explanation of the resistance acquired in the later stages of experimental hyperparathyroidism in rats was that the hormone eventually led, not to the formation of osteoclasts (that is, cells which destroy bone) but to the proliferation of osteoblasts which build new bone tissue.

The following experiments were planned to determine whether these changes in the histological reaction of the bone appeared at the same time as the changes observed in the calcium excretions and serum calcium—that is, whether the osteoclastic reaction (osteitis fibrosa) changed into an osteoblastic one (marble-bone formation) at the same time as the increased calcium excretion and hypercalcæmia returned to normal levels. We have been interested in such a comparative study of the bone histology

¹ The authors are indebted to Eli Lilly and Company, Indianapolis, U.S.A., for the parathormone used in these experiments.

and calcium metabolism because the demonstration of an exact coincidence in the changes produced would give strong support to the theory that the immunity is merely the result of a change in the reaction of the osteogenic tissue to the hormone.

METHODS.

Rats of Wistar strain, 110–115 days of age, and weighing 175–225 g., were used in the experiments. The diet and methods for determining calcium in the urine and blood were those described by Pugsley [1932]. Each rat received 20 units of parathyroid hormone daily during the experimental period, the beginning of which is marked by an arrow in Fig. 1. Histological studies of the bones were made on the group of rats used in following the excretion of calcium in the urine. One animal was sacrificed each day during the experimental period for these studies. The serum-calcium values were obtained from a different group of rats kept under identical conditions and also receiving 20 units of the hormone daily. The results of the serum-calcium determinations are shown in Table I, and the average values represented graphically in Fig. 2.

The calcium excretion in the faeces was not followed in these experiments because previous work by Pugsley [1932] showed that it did not run such a consistent course as the calcium excretion in the urine, nor did it display such a striking response to the injections.

DISCUSSION.

The histological examination of the bones of these animals showed, in accordance with our previous findings, that the first reaction of the bone to parathyroid hormone is the formation of numerous osteoclasts. This reaction is quite pronounced 2 days after the administration of the hormone. As the treatment is continued the spindle-cell proliferation becomes more pronounced, until on the fourth day of administration the picture obtained is as seen in Fig. 3. The formation of numerous spindle-shaped osteoblasts in the bone marrow is a constant feature of osteitis fibrosa, and the present series of experiments shows that their appearance does not interfere with the increased calcium excretion or the rise in serum calcium. It was found that during the period where both osteoclasts and osteoblasts are increased in number the calcium excretion remains at abnormally high levels. However, the disappearance of the osteoclasts, which was observed on the ninth to twelfth day of treatment, coincided exactly with the return of the calcium excretion and the serum calcium to

TABLE I. Effect of daily administration of parathyroid hormone upon the serum calcium of rats.

Days of administration	No. of determinations	Serum calcium		
		Highest	Lowest	Average
Control	40	10.7	9.6	10.3
1	3	11.2	10.8	11.0
2	3	13.9	13.2	13.5
3	3	14.6	13.4	13.9
4	4	14.4	13.9	14.2
6	3	15.1	12.6	13.8
10	4	11.8	11.3	11.6
12	4	10.9	10.4	10.6
17	5	10.4	10.1	10.2

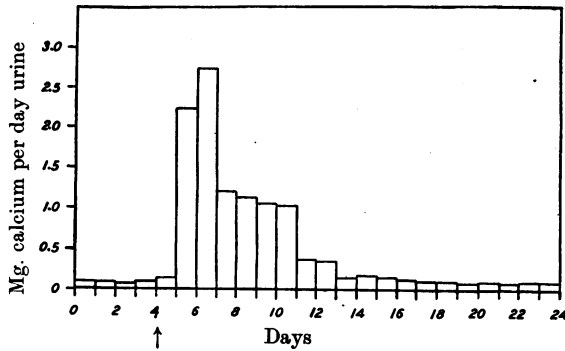


Fig. 1. The effect of administration of 20 units of parathyroid hormone per day upon the excretion of calcium in the urine of adult rats.

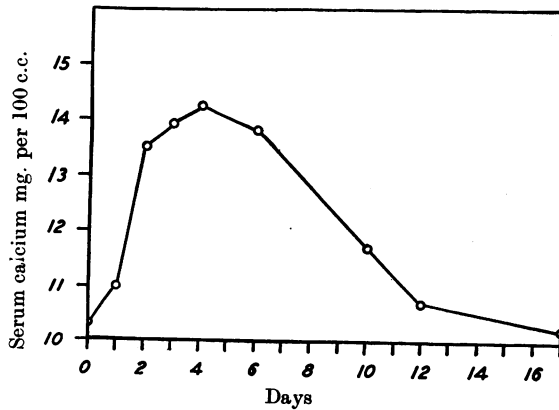


Fig. 2. The effect of administration of 20 units of parathyroid hormone daily upon the serum calcium of adult rats.



Fig. 3. Histological picture of bone on the fourth day of parathyroid hormone administration. Thick layers of spindle-shaped osteoblasts surround the bone tissue; at the same time numerous osteoclasts have been formed.

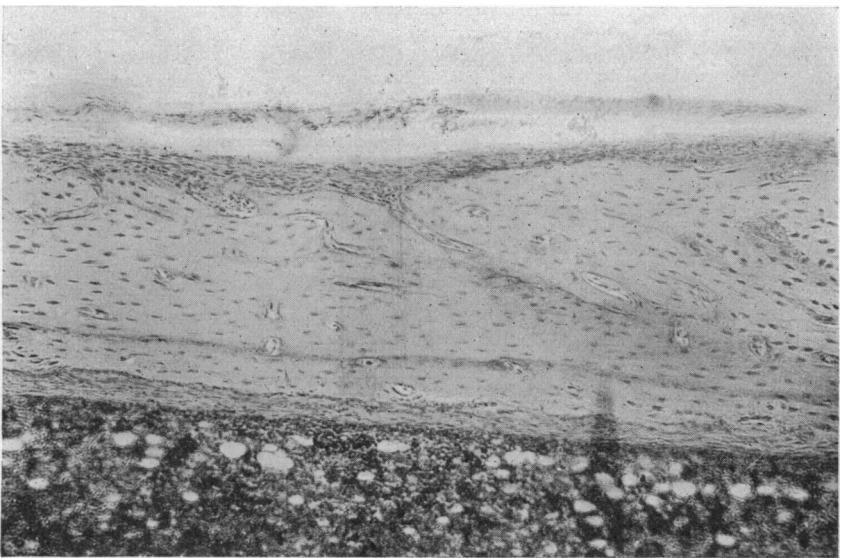


Fig. 4. Histological picture of bone at the eleventh day of parathyroid administration. The osteoclasts have disappeared and only osteoblasts can be seen.

normal levels. On the fourteenth day the bone picture was that shown in Fig. 4. Here we find the bone trabeculae surrounded by many layers of more or less spindle-shaped osteoblasts and practically no osteoclasts are present. If the treatment is discontinued at this stage the bone structure returns to normal; if it is continued the osteoblasts increase in number and lead to the formation of huge amounts of bone tissue, so that the typical picture of "marble-bone" results [Selye, 1932*a*, *b*].

SUMMARY.

A comparative study of the changes produced in the histological structure of the long bones and the calcium metabolism of the rat has been made. It was found that the return of the previously increased calcium excretion and increased serum calcium to normal levels in the later stages of experimental hyperparathyroidism coincides exactly with the disappearance of the osteoclasts in the bone marrow.

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REFERENCES.

- Pugsley, L. I. (1932). *J. Physiol.* **76**, 315.
Selye, H. (1932*a*). *Endocrinology*, **16**, 547.
Selye, H. (1932*b*). *J. Amer. med. Ass.* **99**, 108.