

This Week's Citation Classic®

Klein D C & Raisz L G. Prostaglandins: stimulation of bone resorption in tissue culture. *Endocrinology* 86:1436-40, 1970.

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The effects of several prostaglandins (E1 and E2) on the stimulation of bone resorption were compared to those of parathyroid hormone. The prostaglandins caused increased release of previously incorporated radioactive calcium into the medium, losses of stable and labeled Ca from the bone, and morphological changes of osteoclastic resorption. [The *SCF*® indicates that this paper has been cited in over 445 publications.]

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As I was finishing my PhD work with Roy Talmage at Rice University, I decided to continue my *in vivo* studies on the hormonal control of bone metabolism using *in vitro* methods. Larry Raisz had developed one of the best *in vitro* bone systems, so I contacted him and we started working together in July 1967 at the University of Rochester.

The specific stimulus for this *Citation Classic* came directly from Van Chase and Gerry Aurbach at the National Institutes of Health (NIH). They had found that prostaglandins elevate cyclic AMP production in the embryonic bone^{1,2} but didn't have the proper experimental system to test the effects of prostaglandins on bone resorption. At a meeting they told Raisz about their discovery before it was published and encouraged Raisz to test the effects of prostaglandins in his system. We already knew that cyclic AMP stimulated bone resorption.^{3,4} The next logical step was to determine if prostaglandins did.

We found that prostaglandins E1 and E2 were highly potent, having effects generally similar to those of parathyroid hormone. In the report we speculated that prostaglandins might be involved in pathological bone resorption, a difficult clinical problem

with devastating effects. It is associated with rheumatoid arthritis and can occur in skeletal tissue adjacent to tumors, or near inflamed and infected tissue. Our *in vitro* finding provided investigators with the basis of a simple hypothesis to test, i.e., that prostaglandins may be responsible for pathological bone resorption.⁵ Citation of this report in part reflects the testing of this.

Further stimulus for continued interest in this area came from Raisz's finding that bone tissue produces prostaglandin E2 and from subsequent reports that this is stimulated by a variety of factors that influence bone, including mechanical stress, parathyroid hormone, growth factors, and interleukin 2. In addition, Raisz's group has found that certain steroids that inhibit bone resorption might act by inhibiting the local production of prostaglandins.^{5,6} Thus, two other reasons that this report has been heavily cited are that prostaglandins appear to play a fundamental role in bone resorption and that Raisz is still adding fuel to the fire.

I decided to leave the bone field while still at Rochester. I felt that this area was overcrowded with mature laboratories, and I wanted a bit more elbow room. While casting about for new horizons, I heard a lecture on "The truth about the pineal gland" by Russ Reiter. The truth was that there was not much known about it but that it seemed interesting. Accordingly, I decided to work on the pineal gland. Raisz supported my decision, and I started off on the pineal gland, which remains my main research focus. My first experiments were to determine if Raisz's organ culture system would work with the pineal gland. It worked fine, and this explains why one of the more popular culture media used for pineal glands came out of bone culture studies.

My pineal work at Rochester was supported by NIH funding intended for Raisz's bone work. It seems that Raisz's decision to support my pineal work turned out to be a good one: it led to a *Citation Classic* on pineal N-acetyltransferase.⁷ Perhaps granting agencies who want to defend their willingness to give investigators freedom to use funding according to their best judgment might want to cite this set of events as further proof that this policy can work out very nicely indeed.

1. Aurbach G D & Chase L R. Cyclic 3',5'-adenylic acid in bone and the mechanism of action of parathyroid hormone. *Fed. Proc.* 29:1179-82, 1970. (Cited 55 times.)
2. Chase L R & Aurbach G D. The effect of parathyroid hormone on the concentration of adenosine 3',5'-monophosphate in skeletal tissue *in vitro*. *J. Biol. Chem.* 245:1520-6, 1970. (Cited 270 times.)
3. Vaes G. Parathyroid hormone-like action of N⁶,2'-O-dibutyryladenosine-3'5' (cyclic)-monophosphate on bone explants in tissue culture. *Nature* 219:939-40, 1968. (Cited 115 times.)
4. Raisz L G, Brand J S, Klein D C & Au W Y W. Hormonal regulation of bone resorption. (Gual C & Ebling F J G, eds.) *Progress in endocrinology: proceedings of the Third International Congress of Endocrinology*, 30 June-5 July 1968, Mexico, D.F. Amsterdam: Excerpta Medica, 1969. p. 696-703.
5. Raisz L G & Martin T J. Prostaglandins in bone and mineral metabolism. *Bone Miner. Res.* 2:286-310, 1983.
6. Feyen J H M & Raisz L G. Prostaglandin production by calvariae from sham operated and oophorectomized rats: effect of 17 β -estradiol *in vivo*. *Endocrinology* 121:819-21, 1987.
7. Klein D C & Weller J L. Indole metabolism in the pineal gland: a circadian rhythm in N-acetyltransferase. *Science* 169:1093-5, 1970. (Cited 465 times.) [See also: Klein D C. *Citation Classic. Current Contents/Life Sciences* 31(2):16, 11 January 1988.]

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